Reply

Because answering line-by-line to the OA carries the risk of our replies being "chopped up" to bits and pieces and thus – in following the PTO's train of though appearing "disorganized" (in the word of the PTO) we would like to address some of our specific replies upfront:

This will also summarize the main points made by the PTO and show that the PTO had unconvincing line of reasoning.

1) The examiners have stated, that there is nothing non-obvious in the applicant's invention as it relies on information that was all known in prior art. Therefore – the PTO argues – the invention is prima facie obvious over the prior art. We have to traverse this false conclusion with several facts and an analogy.

1a) Please consider the following relevant analogy. It is notable that Sikorsky and his inventions (yes he is named inventor) is displayed in the Smithsonian Museum. Also the Science TV channel (Big, bigger, biggest – February 2010) had a show about airplanes, and about the invention of Igor Sikorsky. The problem of that time was that the engines could not lift enough weight. So Sikorsky was solving the problem (unsolvable by others) of putting not 1 but 4 engines on the plane. That came with the consequent problem that if one of the engines failed the plain went into a spinning and crashed. Sikorsky solved that problem by putting the engines as close to the center as possible and putting a rudder on the tail plane. Voila, the invention was born. (Coincidentally this is also interesting for me as I had Sikorsky ancestors who left Poland generations ago, although I'm not a descendent of the above named inventor).

Using the same argument that the PTO used against our invention, all the elements of Sikorsky's invention was "known" in prior art. It was known that more power can lift more, if you have 4 horses in front of the carriage it can pull more. So, four engines would be more powerful then one. The rudders were used in boats before and it was also known that if only one sail (or the spinnaker) was up and the wind was turning (spinning) the boat, the rudder could compensate to that. Yet no one doubts that Sikorsky had an invention. [A somewhat similar argument could be raised for the helicopter. It was known that the propeller would propel a plain forward, so if it is turned upward with a

bigger blade, it would give a propelling force upward. The spinning caused by the rotor (propeller) upward could be compensated by a smaller propeller sideway to counteract the spinning, as horizontal movement was achieved before in airplanes.] *According to our PTO examiners if all elements were known in prior art there would be no invention.* In fact if we would use the same false conclusion and unconvincing reasoning that was provided by the PTO against our invention – the PTO could have said that the prior art in Sikorsky's case could and would have known all these elements and simply "chose" not to use it. (Note I'm using the same "chose not to use" phrase that the PTO did giving an "argument" or rather an opinion in evaluating our invention).

I think, this argument by the PTO would be as absurd in the Sikorsky's analogy as it is in our invention.

1b) The book "Patent it Yourself" (by patent attorney David Pressmen 10th edition 5/24) under patentability flowchart also reveals that (if the invention is in the statutory class, composition/new use; it is useful; has novelty (new combination or new use of old feature); provide a new and unexpected result and if the answer to that is yes or possibly [yes] but it has: one or more secondary indicators of un-obviousness; (if it is a combination individually old features and has synergism); and #17 over three references would have to be combined to show the invention, the PTO is **very** likely to grant a patent.

So just because the invention relied on prior art, (if a number of prior art references had to be combined to come up with the invention) but the invention has made conclusions that others did not and others could not make, and a number of secondary factors also supporting this, then the reliance on prior art does *not* excludes the invention from patentability!

So the PTO's reasoning that if "all the elements were known in prior art" that fact would preclude patentability is incorrect in two different ways. For one it is incorrect based on the above references and examples. Second, it is incorrect because the PTO's statement of "all the elements known in prior art" would also have to inherently imply that the same conclusions that this inventor made and the enablement he have given (or in this case

according to the PTO the same element of the enablement) was also known in prior art. This is clearly not the case, and the PTO has failed to provide any prior art showing that. In fact the secondary factors precisely point to the exact direction that the PTO made erroneous conclusions! To this argument the PTO's strategy was to disregard the secondary factors. No one but this author have drawn the conclusions needed for this invention and no one enabled the invention before this author in order to overcome the obstacles set by divergent guidance and strong teaching against. So the PTO's said statement is clearly erroneous and it is clearly not supported.

(We refer back to prior discussion to how many factors we needed to consider for the enablement. In addition to our utility please refer to our amendment to the specification submitted on April 28, 2008 [as reply to the 3rd OA]).

1c) Furthermore, the same book [Patent it Yourself (by patent attorney David Pressmen 10th edition 5/16 second column)] said that 'one influential court said that unobviousness is manifested if the invention produces "unusual and surprising results".' We have mentioned in our replies (e.g. p.191 of our March 11 2009 reply) that more lives could have been saved by our invention since the beginning of our application then the fatalities of the worst infectious epidemics of all times. (Even if we are erring 50% in that assessment that is still an enormous achievement). What does this fact speaks for if not an unusual and surprising result? This fact emphasizes the importance and the magnitude of the invention. [The PTO carefully avoided and never commented on that statement (and that analogy for this unusual and surprising result) that we brought up in our previous reply]. [We turned for a patent publication as we felt that otherwise we would not be able to get the interested parties to become motivated to propel a change for the application of our method.]

2) We have mentioned in our prior replies that the cited prior art (like the Chappell reference and others) were not enabled for the use of our claims. The mere mentioning of suggesting to use the combination treatment for a broad category (and all inclusive category of depression, or all mental illnesses, or for all neuropsychiatric disorders) without discussing or mentioning of how to overcome the obstacles and current teaching

against in the prior art would not have placed the "invention" in the hand of the skilled in the art as he/she could have not been able to overcome said obstacle. (There is another – even stronger – argument for the non-enablement of prior art that we will discuss later). The PTO examiners in their replies ignored the presented fact and simply kept repeating without reasoning that the artisan would have known how to use the combination because combining medications is within the practice of the skilled in the art. (It is true that the combination treatment had been in use for other disorders like for psychotic depression, or even treatment resistant depression (TRD), but the guidelines in these cases were clearly different with no strong teaching against, with no divergent guidelines for these other cases, and with a different risk benefit alternative analysis). The same cannot be said for non-psychotic (non-TRD) unipolar depression as initial treatment (that is using our exclusion criteria for the purpose of our claims). So the PTO's opinion is simply a non-convincing reasoning. The PTO did not accept our above reasoning, and did not have any rational counterargument of why our reasoning would not stand. Instead the PTO (incorrectly) argued that "anybody" could have had the same conclusion, enablement or the same risk/benefit analysis as this applicant had [the point is that with diligent work others possibly could have but did not!] The prior art did not made any mention to the same or any risk benefit alternative analysis. The invention was not obvious and could have not been obvious for the prior art, no one ever though of it (no one ever published it), no one came to the same conclusions, no one ever combined a multitude of prior art elements in support of he said conclusions and in order to to overcome the existing strong teaching against the method and the 'at the time' existing divergent clinical guidelines. (All of these were presented to the PTO before).

The PTO's speculation to "defend" against these facts by stating that others would have known the invention but simply have "chosen not to use it" in order to save lives sound ridiculous to me and it is an unconvincing line of reasoning. Any invention (the best of the best) could be rejected with this kind of false argument of "sure others could come to the same conclusions and enablement but have chosen not to"!

I just cannot comprehend of how the PTO can keep insisting that this line of "logic" would be convincing and appropriate ground for rejection.

This kind of "logic" is also reminiscent of the reported historical statement made by one of the former Commissioners for patents wherein the PTO insisted that "all that could be invented was already invented", and suggested to the Congress dissolving the patent office. Since then we all enjoy the benefit of new inventions and life would not be the same without them.

So as we said our invention was not obvious and could have not been obvious for the prior art, no one ever though of it (no one ever published it), no one came to the same conclusions, no one ever combined a multitude of prior art elements in support of he said conclusions and in order to overcome the existing strong teaching against the method and the 'at the time' existing divergent clinical guidelines. In turn to this strong argument it is my recollection that the PTO said that it is not of the PTO's concern if the artisan have or have not used a method that at the judgment of the examiner should have been obvious, and it is of not the PTO's concern (or jurisdiction) that many lives were wasted in wane because the method of the applicant's invention was "chosen" by the skilled of the art to be never used in prior art. This type of false logic by the PTO assumes that the field of healthcare and the medical profession operates under the auspices that if it is known that a method can save lives at great magnitudes (you have an enablement for the method and a beneficial risk benefit ratio, etc) then everybody would "chose" of not saving the lives, but ignorantly and maliciously "kill" people just because. This is again an absurd and shocking "conclusion" directly deriving form the statement made by the PTO. Therefore the PTO definitely had an unconvincing reasoning, and therefore the claim rejection based on that must be withdrawn.

The PTO basically also said that they do not care if the artisan's so called "choosing" of not to use the otherwise "obvious invention" creates a scandal or major lawsuit for the drug companies as that is not of the PTO's concern. It sounds from the PTO's OA that it is not important of what all people who were skilled in the art thought and showed with their behavior (of not saving lives) but what is important that the PTO examiner (who is not a clinician therefore not skilled in the art) can maintain that strange "logic" no matter how ridiculous that sounds! I just cannot comprehend that line of irrational reasoning. (I admit this is totally irrational to me!)

3) The secondary factors we listed for supporting unobviousness were totally ignored first by the PTO, much later they were minimized (I think to the acknowledgement of a single factor) and last conditioned that these (strong) secondary factors do not apply in this case for patentability. The fact that these secondary factors also contradict the statements made by the PTO was simply disregarded.

4) As regards to revisiting 2) and 3) above: In the most recent OA pages 43-54 the PTO recites that:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.
In other words, in order to be enabling, a patent disclosure must enable one skilled in the art to practice the invention."

Clearly, the cited prior art references (like Chappell and others) with mere mentioning of suggesting to use the combination treatment for a broad category (and all inclusive category of depression, or all mental illnesses, or for all neuropsychiatric disorders) without discussing or mentioning of how to overcome the obstacles and current teaching against in the prior art would not have placed the "invention" in the hand of the skilled in the art as he/she could have not been able to overcome said obstacle. There is also a proof for that that is supported by the fact that these are only patent publications and not issued patents and none of the cited prior art had any experimental data in regards to the claims made by this applicant. [All these prior art references also disregard key factors presented later under 4c)].

We have mentioned several times (like reply to the 1st OA page 60 last two paragraphs) that:

In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. **"A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."**
"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).) (cited in page 200, Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003.)

The PTO always ignored these patent rule references, and not commented on those. I do not know what prompts me to repeat these and expect a different result from the PTO, but I think that if the PTO examiners – with their own admission feel that the applicant responses indicate that he is misunderstanding the standards of patentability, and if the applicant is quoting from a patent book, then the PTO ought to go into detailed explanation and the PTO is expected to reply very specifically to this and similar arguments made by the applicant.

The PTO (on page 49 of last OA) is also continuing, that while the patent disclosure must enable one skilled in the art to practice the invention the PTO argues that the patent rules are distinct from the FDA and legal standards to practice medicine (and avoid malpractice) in which (for patents) "the only requirement is that the application place the public in possession of the invention".

Please note that

4a) the cited prior art references did not place the public in possession of the invention (as far as the applicant's claims), as they did not overcome the said obstacles [divergent guidelines, strong teaching against, and other considerations mentioned under 4c), etc] to practice the invention, and they made only a mere mentioning of a very wide diagnostic category without experimental data and without any attempt for enabling. The secondary factors are all supportive of these statements.

In addition,

4b) The applicant only had to show that the examiners had an unconvincing line of reasoning in order for the claim rejection to be withdrawn. The examiners did not have a convincing line of reasoning for the cited prior art being enabled for our claims. (As stated at pages 18-19 reply to 2nd OA):

"The PTO also disregarded the strong supporting secondary factors (pages 93-99) and additional paragraphs of the referenced law (page 98 lines 15-40). Namely, and in putting all of our arguments together (see also page 98 lines 23-31) **the examiner did not "present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references" if the PTO assumes in the PTO's reasoning that the artisan would skip clinical steps and be willing to commit malpractice in order to follow the PTO's unconvincing line of reasoning.** (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

There are important factors to consider as regards to the prior art like the differences in the function of the invention (In re Ellis, 476 F.2d 1370, [C.C.P.A. 1978].) (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 223). Our claims are aiming a different patient population and a new use.

The skilled in the art would be discouraged in following the path (that the PTO recommends) or would lead in a direction divergent from the path that was taken by this applicant. (In re Gurley, 27 F.3.d 551 [Fed. Cir. 1994].) (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 224)."

4c) The PTO continues in the most recent OA (page 49-50):
First the PTO argues with a dissimilar example of rofecoxib (Vioxx®) that had been withdrawn due to said lawsuit and associated side effects about which the facts were hidden by the manufacturer. The PTO argues that if somebody would submit a claim for using the same compound for same use that would be rejected, and I (and all laymen would) agree with the validity of said statement in that particular example. However, the invention of this applicant is different in many ways. The applicant is presenting a combination use for new use (e.g. our exclusion criteria for initial treatment of said depression), and we will further elaborate on these differences in a little while. The PTO (incorrectly) argues that the combination of antidepressants and antipychotics are "not currently used in clinical practice as first-line therapy for depression" [I'm assuming the PTO meant the same depression category as in our claims], "because of concern over adverse effects" [just as in case for rofecoxib (Vioxx®)]. The PTO continues that *"in order for a reference to be non-enabling, there must be a clear teaching in the art casting doubt on whether the skilled in the art would be able to practice it, not merely evidence that one skilled in the art would decide not to practice it".*
While to show that the PTO erred we would use a distinct argument giving quite precisely what the PTO requested, but it is notable that the PTO did not list PTO regulations or applicable law to support that above statement.

We have mentioned – giving reference in our utility – that there is a distinct difference between the categories of depression in which the combination therapy was used in comparison to giving the combination treatment for initial treatment for non-psychotic, non-treatment resistant unipolar depression. **Therefore no prior art reference ever shown that the combination treatment would be effective for the new use set in the instant claims!**
This should sufficiently address that the instant case is dissimilar from the example shown by the PTO and is very much patentable.
All the other depressive categories where the combination treatment (and the antipsychotics) has been in use involved psychosis and that had been clearly stated in prior art even for <<"non-psychotic"-treatment-resistant-depression, wherein the prior art stated that the cause of the said treatment-resistant-depression may be the unrecognized psychosis". >>

It was also shown that no prior art reference actually used the combination for the purpose of our claims (for example as initial treatment for reducing the risk of suicide; for inhibiting the paradoxical effect of antidepressants worsening depression and causing suicidal ideation or suicide).
The PTO stated that *there must be a clear teaching in the art casting doubt on whether the skilled in the art would be able to practice it* [the method, the combination treatment with the use of atypical antipsychotics and dopamine system stabilizers for categories other then those involving recognized or unrecognized but underlying psychosis]. **This doubt had been clearly presented in our utility with the prior art references**:

To elaborate more on this let us point to the appropriate references in our utility (that had been rehearsed many times in the replies to the OAs as well):

From page 3 lines 21-24 of our utility:
"Nierenberg (Nierenberg. A. A., 1992) had noted that the cause of treatment-resistant depression may be an unrecognized psychosis, that may explain – at least in part – of why the "treatment-resistant" depression group improved with the addition of an antipsychotic medication."

From page 13 lines 30-32 of our utility:
"Depression in psychosis (including psychotic depression), and depression in bipolar disorder (**where psychosis is often predominant**) are different categories from MDD or depression without psychosis."
From page 30 last paragraph with font 14 to page 31 first paragraph of our provisional application, re-entered as amendment to the specification in the reply to the 2nd OA page 120:
"Obviously when *both psychosis and depression are present like in schizoaffective disorders, psychotic depression*, or even at times in bipolar disorder, both groups of medication are indicated and used, targeting the depressive or psychotic symptoms respectively. (**About 2/3rd of patients with *bipolar (manic-depressive)* disorder are having a history of at least one psychotic symptom. Bipolar patients who are psychotic during one episode of affective illness are highly likely to be psychotic during subsequent episodes.** [Tsai, SY. M., et al. 2002.]). Antipsychotic medications also showed a value during the manic phase of the bipolar disorder. (See Miller, D. S. et al, 2001, Yatham, L.N. 2002, Sajatovic, M. et al. 2001.).
It has been also shown, that about 15% of major depressive disorders, usually those with *melancholic* features, develop into delusional (psychotic) depressions. (Akiskal, H.S. page1137, 1995)."

This above distinction is also **an evidence** that the present claims are somehow distinct from the prior art. This evidence was based on prior art. So the **secondary considerations** not only prove that the PTO had an unconvincing line of reasoning leading to claim rejection; but also show that new considerations differentiate the instant invention and claims from prior art, and can overcome "prima facie obviousness". Actually, there is no "prima facie obviousness".

Less importantly we have also stated:

From page 1 lines 30-to page 2 lines 1-14 of our utility:
While chlorpromazine was used early on in the treatment of depression, as tricyclic antidepressants became available the use of antipsychotic medications declined, and they were never widely used in the treatment of depression in the absence of psychotic symptoms. See also Raskin A. et al 1970, p.170: "There is a persistent belief that these drugs (antipsychotics) are not very effective in the treatment of depression". In general, the use of antipsychotic drugs was reserved for use in patients having psychotic symptoms. It was generally accepted that antipsychotic drugs used alone could not treat major depressive disorder. In fact, it was thought that antipsychotic drugs, including some of the atypical antipsychotics, may even have depressogenic properties. (Harrow, M. et al 1994, Galdi J. 1983, Tollefson, G.D. et al 1998, Maguire, G.A. 2002, Cookson I.B. et al.)
In contrast to antidepressants, antipsychotics alone (including the atypical antipsychotic risperidone) were ineffective in the chronic mild stress (CMS) model (animal simulation of depression) (Papp, M. et al 1996; Papp, M. et al 2000). In sum, many studies showed that antipsychotics do not have significant antidepressant activity and, if anything, may cause a depressogenic effect.

From page 4 from lines 22 and the last paragraph of our utility:
"Thus, to date, the use of atypical antipsychotic medications has been restricted to their use in combination with antidepressants, for the treatment of the following subtypes of illness: schizoaffective disorder; psychotic depression; bipolar (manic-depressive) disorder; and treatment-resistant depression. In all of these categories, the use of antipsychotic medication may be expected due to its effects on contributory psychosis, or severe agitation.
There have been no reports recommending that the combination therapy can or should be used for a major depressive disorder, or for other depressions as an initial treatment, upon initial presentation to a health care provider (or as soon as possible), or for using the combination as a treatment of first choice, for reducing the risk of suicide."

It is true that we also mentioned side effects, but the focus in the reply is now on the difference of the depression categories:

Page 2 lines 15-18 of our utility:
Due to the severe side effect profiles of the traditional antipsychotic drugs, the risks of taking these drugs, in the absence of their specific indications (such as psychosis, severe agitation or anxiety) were believed to be unwarranted by the medical community. (Price, L.H. et al. 2001. p. 207.)
Page 2 lines 25 to page 3 lines 10 of our utility:
Early reports compared the antidepressant efficacy of two older/traditional groups of medications, the tricyclics (TCA) and traditional antipsychotics, or their use in combination, (Robertson, M., et al. 1982; Hollister, 1967). This review by Robertson (Robertson, M.M. et al. 1982) was based mostly on studies with mixed-anxiety depressive states, now more appropriately called as depression with anxiety as a comorbid disorder (Zimmerman, 2002). The combination use had been reserved for psychotic depression. A later review summarized the opinion, that "while a 'true' antidepressant effect has been demonstrated for the tricyclic antidepressants, similar effects appear doubtful for the antipsychotic drugs." (Nelson, J.C., 1987).
The combination use of these medications to treat non-treatment resistant, and non-psychotic depression was never recommended. A book chapter reviewing this topic from year 2001 makes the point that "the risk/benefit ratio in refractory patients lacking such features [as near-psychotic rumination or marked psychomotor agitation] generally does not favor [antipsychotic augmentation]". (Price, H. 2001,). The reports available up to date have reserved the combination use of antidepressant-antipsychotics only for psychotic depression, or for treatment-resistant depression.

So we have clearly stated before relying on prior art that all the other depressive categories where the combination treatment (and the antipsychotics) has been in use **involved psychosis** and that had been clearly stated in prior art even for <<"non-psychotic"-treatment-resistant-depression, wherein the prior art stated that the **cause of the said treatment-resistant-depression may be the unrecognized psychosis**". >> In all those instances the use of an antipsychotic is evident. That is not the case for initial treatment for depression (with our exclusion category). So the fact is that by mere mentioning broad diagnostic categories of depression, all mental disorders, all neuropsychiatric disorders, without any elaboration and without any experimental data (in particular to the use of our claims) the prior art references were not enabled! This is a fact that the PTO did not contest and did not explain otherwise. The example the PTO gave in the last reply does not fit in the instant claims for the reasons explained above.

(See reply to the 2nd OA page 26 second paragraph): We state it again that:
"Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 201 also notes that: "even if an act or document constitutes prior art under Sec.102, it will not bar patentability of [our] claims unless it anticipates [our] claims. ...
Anticipation only occurs if the prior art reference [is] teaching each and every element of our claims. If [we] are successful in arguing [- and we think we gave more than enough evidence for that-] that **the reference does not anticipate [our] claims (because it is distinguishable), [we] will be removed that reference as 102(a) prior art bar to the patentability of [our] invention.**"
In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public..."

As we have shown the prior arts cited do not anticipate our claims. We have also shown the secondary factors that the prior art teaches away.
(pasted from the same reply to the 2nd OA a bit later changing the order):
"A reference teaches away when a person of ordinary skill, upon reading the reference, would be lead in a direction divergent from the path that was taken by the applicant. (In re Gurley, 27 F.3d 551 [Fed. Cir. 1994].) (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 224). ...

The same reference by Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) discussing obviousness (35 U.S.C. Sec. 103(a)) at page 219 states (referring to MPEP Sec. 706.02(J).) "that references must ... suggest [our] claimed invention, or [the] examiner must present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." ...

Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 220 also states, that: "The prior art reference ... must teach or suggest all [our] claim

limitations." **As we have shown it previously (including the secondary factors) that this is also not the case.** ...

the PTO did not present a convincing line of reasoning for obviousness, and therefore the rejection should be withdrawn. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219). ...

Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 222 teaches that in overcoming rejection based on obviousness, we can argue (and in our prior reply I think there is no doubt that we successfully did that) that "the combined teaching of the cited **references still fail to fully teach the invention recited herein**". At page 223 it sates: "**If the references are not each directed toward solving the same problem to which the invention is also directed, then the rejection should be withdrawn.** (In re Rouffet, 149 F.3d 1350 (Fed. Cir.1998).)

The PTO have ignored these cited references, the cited law, and our arguments."

5) The PTO is using non-prior art reference as a "prior art" in rejecting our claims.

On page 51-52 of the last OA the PTO argues that the references we provided (in our reply to the 4th OA page 128) (**Reeves** H et al Efficacy of risperidone augmentation to antidepressants in the management of suicidality in major depressive disorder: a randomized, double-blind, placebo-controlled study. J. Clin Psychiatry 69:8 **August 2008**) would provide a solution for the "alleged failure of the art to propose a solution to the paradoxical effect of antidepressants causing suicide".

First of all this is **not** a prior art it is clearly stated the publication date to 2008 being years after our utility application. **Second**, the cited article does not even mentions the antidepressants causing paradoxical effect and causing depression and suicide.
The PTO cannot list this reference on the basis of claim rejection, this is clearly erroneous.

In addition the applicant did not have a "speculative" line of reasoning, he have collected and made conclusions from a vast numbers of prior art document providing the evidence and enablement needed for the skilled in the art to practice the invention and even to overcome said barriers. It is notable that first the PTO examiners (in disregarding the disclosure) complained of "lack of theory", later when the arguments and facts are pointed out to them they call it "speculation".
The PTO also made an implication - as if this applicant would have requested - that if others got an issued patent based on error 'he should too' – and this is an incorrect statement that was never made or implied by the applicant. However, the applicant feels that when there is such a gap in the understanding between the PTO and the applicant, the PTO should make every effort to address the applicant's concerns, and also strive for

improvement so that the applicant(s) would not be burdened with such an unproductive evaluation process, so that the applicant would not feel ignored and so that the PTO would not just keep pasting the same comments from prior OAs but would actually address the concerns raised by the applicant. The PTO is expected to help the applicant without attorney representation and not to overburden him with statements that are simply not true and references that are not even a prior art documents (See for example the notes about the Reeves non-prior art reference shown above).

6) The PTO (also) erroneously states that the applicant has double standard regarding his and others' work.

The PTO just does not get it when it comes to discussion of what constitutes a malpractice (violating the standard of care), and how the standard of care can (and should) change with new information disclosed by the applicant. The PTO keeps repeating that **if** the Chappell, the other cited prior art references, and the skilled in the art would have made the same conclusion along with the same explanation as the applicant has in his disclosure, then they too would not have committed malpractice when deviating from clinical guidelines and the strong teaching against, then they too would have been able to use the method for initial treatment. The PTO further assumes that all these other entities just "chose" of not to do that. The PTO makes it sound as if the prior art would have been in the possession of the applicant invention with full disclosure. The PTO assumes that the skilled in the art was in possession of the applicant's new risk benefit alternative analysis and all the rationals supporting that new analysis. This is simply not true (as the secondary factors show)!

The prior art has also made clear statements of the (recognized or un-recognized) psychosis component whenever the antipsychotic and combination treatment) was used. The initial treatment for MDD (with our exclusion criteria) therefore is distinct from all other instances when the antipsychotic or combination was used before.

Again, the PTO assumes that the prior art and the skilled in the art just "chose" of not saving peoples' lives. The PTO further concludes [when secondary factors are brought up showing the liability of the entities of risking people's life of not coming forward with the information of the invention and not applying it to practice (and further research)], that it is not the PTO's business of worrying about if people are using or not what's "already known and obvious". This is a dangerous assumption, and a highly "twisted"

train of thought on the part of the PTO, especially when disregarding presented facts (e.g.4c). It sounds like that the PTO is coming up with these "explanations" (that makes no sense to me) in order to defend their statements. The facts are grossly disregarded by the PTO (as of the behavior of the skilled in the art prior to the applicant's priority date; as of the lack of disclosure by others for enablement for the invention overcoming the barriers, the divergent guidelines, - as the strong secondary factors attest to that). When the facts are shown to the PTO the PTO simply states that it is none of their concern to examine said facts (or secondary factors) and simply assumes that others simply have "chosen" not using the invention.

These erroneous thought processes need to be promptly addressed, as they are unconvincing. As per the cited PTO regulation claim rejections that were based on the examiners' unconvincing reasoning must be withdrawn.

When the examiners' erroneous and unconvincing reasoning is pointed out from a different perspective citing other issued patent(s) – that is that if the examiner's reasoning would be true and convincing, the patent office could have not issued another US patent as the same reasoning of the examiners in this instant case would have also prevented the issuing of that other patent that did issue. The examiners' reaction to that is not to re-examine the validity of their unconvincing argument, but simply to ignore the facts, and state that they do not deal with other issued patents. [see Tollefson references for example and our last reply to the examiners.]

> Of note as a different issue: The examiners also stated that I have no knowledge of the communication between the drug company and the PTO (regarding the other issued patent). That is true, since that information is sealed by the PTO. However, that can be potentially obtained through court just as Irving Kirsch got sealed information from the drug companies based on right to know. I find the examiners' attitude inappropriate for attempting to close an argumentthat is based on that only them have access to that information. However, the applicant's prior argument was convincing even without that sealed data.

Other patents were brought up in comparison, not just to raise a discrimination issue, but also to show the erroneous nature of these examiners's thought process compared to the examiners evaluating the other patents. We did not ask to get a patent issued just because

the PTO (possibly) made errors elsewhere. However, if the PTO made errors in that magnitude in all the other patents we have mentioned in comparison to ours, that would raise a grave concern that should be addressed, acknowledged, appropriately scrutinized, but not brushed off and ignored.

Unfortunately, when we petitioned the Commissioner for patents for procedural errors, raising some of our above concerns (and many others), the PTO did not use any logical or rational arguments of why our presented facts were incorrect, instead the PTO just issued an opinion that all of our statements were not true. It is difficult to reason and to give a counterargument if the PTO only issues an opinion and refrains from any explanation or reasoning. This should not be within the spirit of an evaluation process, nor should that be helping the applicant (who is without attorney representation) as without explanation from the PTO he cannot even *guess* what the PTO had in mind.

So far we have addressed the PTO's thought process and erroneous and unconvincing line of reasoning and in particular countering them saying that there is nothing non-obvious in the applicant's invention as it relies on information that was all known in prior art.

A couple more issues need to be discussed in this regards:

A1) The PTO has swept their comments under one umbrella, and argued for 'inherency' when it came to an effect protecting against relapse, the recurrence of said depression. (e.g. claim 98). It had been known (and disclosed in the specification) that there have been guidelines of how long an antidepressant should be given, (and if the antidepressant is discontinued too soon a recurrence relapse would occur). So indeed, a method different from ours that would suggest continuing the antidepressant to avoid recurrence relapse would not be novel, and would also be "inherent" to protect against recurrence relapse). That would be even obvious for a layman. [That method would fall within avoiding non-compliance to medications, (the skilled in the art is given directions in guidelines of not to discontinue the antidepressant prematurely).] The relapse "prevention" with medications is therefore not used in that sense in the art; and for that term (to be met in the context presented) additional measures then just continuing the antidepressant is

implied or understood. Therefore there is nothing inherent in relapse "prevention" by administering the combination treatment. No prior art has suggested that new use (combination) that it would be "preventive" in comparison to a single antidepressant as only that was customary in the prior art! In the light of what we discussed in how distinct the depression with the exclusion category is from other instances where antipsychotics have been used before, there is nothing inherent for the instant claims.

This gets even more heightened for no inherency for our method of the combination treatment, as when it comes to a solution for a problem about the paradoxical effect of antidepressants causing depression and causing suicide. Therefore giving another class of agent (with our combination treatment – as disclosed) cannot be inherent to solving this problem. The cited prior art like Chappell or the others did not even mentioned this within their specifications or claims. Therefore the rejection was based on unconvincing reasoning. (and the PTO was lacking to elaborate on this element). Under 5) we have discussed that the PTO incorrectly cited a non-prior art reference as a basis of claim rejection, and did this only in the last OA.

A2) The following was also not in the Chappell and other cited prior art references.

Claims (42, 48, 53, 54, 99, 100, 101, 111, 112, 113, 114, 115, 116, 120, 128, 136, 141,) that are addressing for example the method "protecting against (or inhibiting the) development of tolerance towards said antidepressants" or "**avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression, avoiding worsening of said depression from said antidepressant, treating worsening of said depression from said antidepressant and** *said antidepressant* **causing suicidal ideation**".

The PTO did not make any convincing reasoning as for the basis of the said (part) of the claim rejection. Before our reply to the 5th OA the PTO was avoiding even acknowledging that we have had an invention in this regards that was unsolvable by others. In fact we had major arguments – addressing a list of secondary factors – that specifically draw the PTO's attention to that part of the claims, that is that the FDA directors have repeatedly perplexed on their inability to provide a solution to that problem. We even pasted news paper cut outs to our reply so that part was standing out

and could not have been missed. Correction: the PTO did miss and ignore the secondary factors and only much later minimized it to a single factor.

So **if** there is nothing non-obvious in the applicant's invention as it relies on information that was all known in prior art, **how come** the use of our method for the paradoxical effect of the antidepressants causing depression and suicide **is still such an unsolvable problem**? How come the PTO examiners do not see anything patentable and reject claim drafting assistance?

B) Similar arguments can be said about another problem still unsolvable by others:

In our reply to the 1st OA page 64 (under: Consid: A)/2) we mentioned:

> "Recurrent Brief Depression (RBD) that lacks the 2 week requirement for MDD, had been researched before our applications.
> It had been described that fluoxetine had the same rate (or no effect) on the recurrence rate than placebo. Fluoxetine neither raised, nor lowered the suicide attempt rate compaired with placebo [for RBD]. (Montgomery D.B. et al, Eur Arch Psychiatry Clin Neurosci **1994** 244 (4):211-5. – copy is [was] attached).
> The same article also concludes, that RBD has a different pharmacology than MDD."

RBD is under the category of Depression NOS that we included in our specification in our utility.

So if there is still an unsolvable problem (that is the antidepressants are not useful for RBD and for reducing the suicide in RBD) then why would our method with a (potential) claim in this regard not be non-obvious, and how come the PTO cannot foresee anything patentable and thus rejecting claim drafting assistance?

C) As regards to claim rejection for claims 140-145 under "new matter":

> The applicant is puzzled by the "new matter" rejection, especially since the PTO was not specific of what part(s) the examiner was specifically considering as "new matter".
> The applicant is also surprised on the rejection of the claim drafting assistance, as buy changing some of the words to synonyms (in the context) the new matter could be easily avoided.
> The examiners also did not draw attention if a continuation on part would give a solution to said claim rejections. This would and is expected along with claim drafting assistance.

The applicant traverses the new matter objection and the PTO's "supporting" statements: **It was clearly described** in both the specification and the provisional application, **that the health care provider needs to discuss the risk/benefit/alternatives with the patient(s)** and involve them in the decision making.

We were very careful of pasting to the claims the "items/specific considerations" in using the exact phrases used in the specification). **All of these "items or specific considerations" are falling within the risk/benefit alternative discussion, and as such it was disclosed that these need to be discussed with the patients**. If absolutely needed, some of the words discussed can be substituted with disclosed (as we definitely disclosed

these considerations in our specifications). The word "steps" were only used in the claims to emphasize to the examiners the patentability.
If it is felt (for some unknown reason to the applicant) that the word step is the one that the examiners objected to, then that word can be replaced with alternate phrase (like "discussion of the following risk/benefits".

If that is the case, I do not see why the PTO would not see any claims allowable, and why the PTO would not assist with claim drafting assistance. At minimum the applicant needs specifics of what exactly (what words or phrases) the PTO was objecting to.

--

The **PTO has made other errors and had other unconvincing line of reasoning** that would be addressed mostly under the line-by-line reply.
Two of those would be still best addressed here as they were raised under the PTO's "Further Comments" from page 43 of the last OA.
a) One is when at page 45 the PTO revisits that Chappell reference in "teaching" (that is mentioning) that the different D4 antagonists with antidepressants can be used for the treatment of depression and therefore this according to the PTO would render the applicant's invention obvious, as olanzapine is mentioned having a D4 antagonist activity.

(This was discussed previously at reply to the 4th OA page 3 last paragraph, and in particular at page 69 under **#VII of reply to the 4th OA:**
"the PTO examiners have still failed to sufficiently address the applicant's reply to the 3rd OA in particular III/1 and III/9 p.(18-43). Therefore the PTO examiners' statement remains unconvincing. We have **cited documentation that the mere D4 activity does not ensure antipsychotic action**! Just because some agent showed antipsychotic activity in animal models as the Krammer reference attest to that it does not prove antipsychotic action. Just because Chappell recited the antipsychotic olanzapine as D4 receptor antagonist, this is not an assurance that the antipsychotic action of olanzapine would be due to the D4 activity. In fact it is highly likely that if the D4 receptor would be blocked in an experiment with another agent (not having an agonist or antagonist effect on that receptor) olanzapine would still have its antipsychotic effect (e.g. through the D2 receptor). The PTO disregarded the applicant's more detailed argument from the reply to the 3rd OA (p.18-43). The PTO did not show that what percentage of the olanzapine's action would be due to the D4 activity – if any, and if that alone would be sufficient for an antipsychotic action compared to placebo!
It is of note that the historical speculation that the atypical feature of an antipsychotic would be linked to the D4 receptor was not proven and that idea was abandoned.
The fact that Chappell abandoned his application and did not provide enablement for his mere suggestions makes the lack of enablement even stronger.
The PTO examiners have repeatedly ignored the cited law of (e.g. p 36 of reply to the 3rd OA):
In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."

> **"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public,** meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)"

In summary, the PTO would have to show evidence that olanzapine would not have an antipsychotic activity without a D4 antagonistic activity. Otherwise the claim rejection must be withdrawn (since the cited reference lacked enablement) and also because the PTO did not have a convincing line of reasoning (including that the above prior art would be enabled for the purposes of our claims) - in light of the applicant's above reply. The PTO on page 45 revisits the D4 activity without acknowledging the applicant's prior reply or countering it with logical argument in a form that would address the applicant's reasoning and logic.
However, in light of 4) and in particular **4c)** that argument by the PTO was countered above with different convincing reasoning showing that our claims and the depression with our exclusion criteria is clearly distinct from any prior art use of the combination treatment. So for the reason of 4) and 4c) the Chappell reference is again not enabled and the claim rejections must be withdrawn.

b) The applicant has **other complaint(s):**
The PTO thinks that in the previously amended claims (e.g. claims 1 and 2) that talks about "...said method comprising administering to said patient at a time selected from the group consisting of, as an initial treatment, **as soon as possible** and upon presentation of said patient to a physician or other health care provider an effective amount of an antidepressant, ..." the **"as soon as possible"** "does not serve to significantly limit the scope of the claims" ("and can be interpreted many different ways").
This was brought up in the last OA (page 45 lines 6-8) for the first time!!!
That was a previously amended claim! How come the PTO did not make a notice of this before? **Would the final rejection be against the PTO rules since these claims were not amended with the last reply?**
These parts ("as soon as possible"...) for the previous amendments were done by the applicant former attorney (and this applicant has been long lost his attorney representation).
Most importantly, the PTO is raising the concern without explanation to the applicant e.g. of why the PTO thinks that the "as soon as possible" could be interpreted in many different ways? (What different ways?)
The applicant would like to get some guidance and explanation not just a rejection. The applicant does not see that this could be interpreted any differently as it is, that is the "as soon as possible" is still within the timeframe that has been specified at the end of the claim: "wherein said major depressive disorder categorized as non-treatment resistant and [non-psychotic]". (We have given a definition in our specification for what treatment resistant means and what time frame it involves.)
"As soon as possible", the "initial treatment", "and upon presentation of said patient to a physician or other health care provider" puts an emphasis on the beginning of that time

frame that is otherwise limited and described as non-treatment resistant. Actually this is further limiting the preference with that emphasis, putting more stress to the start of the episode (rather then suggesting using the treatment on the last day, that technically still does not fall within the treatment resistant category). The skilled in the art should understand that nobody is talking about milliseconds difference in the "as soon as possible" description, but in the context of the specification the "as soon as possible" may refer to that after gaining the patient's agreement and cooperation and after discussing the risk/benefit alternative analysis... The "as soon as possible" may also refer to the availability of the medication or if the patient declines the medication and there is another chance to re-discuss with the patient the risk/benefit/alternatives, then the "as soon as possible" time period shifts to the next available opportunity. I really do not think that the description of what "as soon as possible" means in this context would create a conflict. Apparently the PTO does see a conflict, so if this concern is maintained the applicant is asking for clarification as he cannot read the examiners' mind. The applicant needs specifics. That explanation and guidance would be appreciated.

--

Q&C) ***Q*uestions to the PTO & further *C*omments as reply:**

To simplify a long list of objections, the applicant reviewed the common element and what may cause a gap between the PTO's and the applicant's understanding. So the clarification of the definition of this common element is essential and is requested from the PTO:

The prior art references cited by the PTO (and mainly):

1) Howard
2) Chappell
3) Pivac
4) Jordan
5) Theobald

All have the common theme of merely mentioning that a particular combination of antidepressant and antipsychotic can be useful for the treatment of depression. (Let's set aside that they talk about a broad diagnostic category that the PTO considers all inclusive).

Q&C-1): So the question the applicant is asking from the PTO is that **what constitutes enablement in these references?** None of these references had any experimental data, none of these references presented any case report, none of these references gave any further references where experimental data or an actual evidence was given to show that the combination treatment was tried out (and worked) for depression other then psychotic, bipolar, or treatment resistant depression (TRD) [wherein for the cause of TRD prior art suggested unrecognized psychosis].

So what constitutes enablement according to the PTO for these references?

It seems that a mere mentioning for the combination treatment is accepted by the PTO for enablement, and the PTO was using the word that these prior art documents "disclosed" that the combination mentioned by them is useful for the purposes of the instant claim –

as if these references would have had full disclosure to overcome barriers of using them for the purpose of the instant claims.
This seems to be at the core of the misunderstanding between the PTO and the applicant. If the prior art is not enabled the claim rejection based on that must be withdrawn (see the PTO rule cited above).
So the PTO needs to clarify if a mere mentioning of a combination would meet the criteria for enablement.

The Applicant's attention was drawn to In re Wands, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.
It seems that the PTO did not apply the same standard in our case, compared to how easily declared (or implied) these prior art documents enabled. Among others the PTO scrutinized our "lack of theory" disregarding that we presented more then just a theory; the PTO scrutinized our disclosure that it is not sufficient (and reduced that only to the hypothetical cases), when in fact we have provided a very extensive disclosure directed towards of how to overcome each step of barriers that can be potentially foreseen. (Let's look aside that the PTO brought against this applicant non-prior art document, misinterpreted that the paradoxical effect of antidepressants causing depression and suicide was solved by others, disregarded first & later minimized the secondary factors, and had numerous unconvincing line of reasoning, that from the clinical standpoint could not be substantiated. Let's set aside that the PTO engaged into a set of self directed questions in order to answering these they could "support" their unconvincing reasoning and false conclusions, and that said set of questions could only be asked by someone who is unfamiliar with the art). It seems that the PTO was pointing fingers at the applicant for alleged "double standard" (not understanding how the applicant's new disclosure can blaze through new trails and change the standard of care/ and thus of what would or would not constitute malpractice with his new disclosure being out in the public); while it seems that the PTO is who applies a double standard with implying enablement for these prior art documents. (When double standard was brought up regarding the evaluation of this applicant and how other issued patents were evaluated (allowing for example the usage of terminology like SSRI in these other patents, when the same use of that terminology is denied for this applicant), the PTO declined to investigate if such double standard was used, or even to look at if their own line of reasoning could have been unconvincing.

By PTO regulation (MPEP, Section 707.07 (j)) (according to book by patent attorney David Pressman Patent it yourself 10th edition p1/2) the patent examiners are specifically required to help inventors in pro se (no lawyer) cases. The PTO can help the applicant by answering that question that seems to be the key in the misunderstanding between them.

Furthermore, since a key factor was not appreciated by the PTO before [the factor that we described under 4) and 4c) above], the application of the combination of antidepressant and antipsychotic was <u>not</u> evident (for prior art) for the depressive category with our exclusion criteria. Therefore the PTO's speculation was unconvincing (wherein that PTO speculation was also disregarding the facts shown by the secondary factors).
This gets even more emphasis (for lack of enablement) as the above prior art references were only mentioning (within a laundry list) general and broad diagnostic categories without any explanation whatsoever, and without any guidance of how the skilled in the art could overcome barriers to use that method (and to get a conviction that the method would work).
The Theobald patent application does not even focus to that topic much as that is a patent application for a transdermal delivery mechanism They too do not go into any

explanation as to enable the skilled in the art to overcome the barriers aside of a laundry list of medications that the delivery mechanism can be used for. No experimental data support their mere mentioning of the medications for the purpose of the instant claims.

Is it enough for enablement for these vague prior art documents' mere mentioning of the combination treatment for a broad diagnostic category, without any further discussion of how to overcome the barriers of using said method (for the purpose of our claims that was not even specifically disclosed by them)? That is the question for the PTO.

(The objections of "in view of Schmidt" or "in view of Roth" references (on D4) for Chappell could no longer stand if Chappell reference is not enabled, and as we have stated above – in our view the Chappell reference is not enabled, it does not place the subject matter of our invention in the hand of the skilled in the art, it does not overcome obstacles and does not provide direction of how to use the method. The skilled in the art could not have use the method in lack of those disclosures – that we did provide, and what the PTO duly asked from us. The issue of D4 receptor was discussed earlier.

Similar conclusions can be drawn "in view of Berman" regarding the use of ketamine. We did acknowledge the antidepressant effect of ketamine, but that fact by itself could not prompt a clinician to overcome barriers to use it as initial treatment without our considerations for overcoming said barriers by said risk/benefit/alternative analysis.)

The PTO has reduced the risk/benefit/alternative decisions and other considerations to "judgment calls" or to "opinions". We traverse this. Without the vast amount of information we presented in order to blaze through a new trail and change the standard of care, and in order to save lives and provide the claimed benefits, the skilled in the art did and could not come up with the "judgment call" and could have not apply the method.

Q&C-(reply)-1b):
At page 2 (lines 22-24) the Jordan reference states that it has not been reported before that compounds in their invention / aripprirazole, have agonistic activity at 5-HT1A receptor subtype. Their "enablement" is restricted to showing that activity of their test compound with a reference compound. (page 18). At page 4 they refer to a WO reference disclosing "5HT1A receptor agonist, buspirone". The Jordan reference does not enables aripriprazole in clinical trials (or in any other ways) of being efficacious for the treatment of depression that they claim (e.g their claim 2, 21, 22; [and in claims 19, 21 drug addiction]. Jordan specifically does not enable aripriprazole for initial treatment or for our other claims. The sole "enablement" is based on, having agonistic activity at 5-HT1A receptor subtype **just like** the compound **buspirone** that was cited by them.

The PTO (in Response to Argument) stated that the fact that those in the art do not use a particular therapy (buspirone) is not persuasive for a finding of non-enablement. The PTO is disregarding the argument, that said "similar compound known" (buspirone) did not have an antidepressant effect (for initial treatment) and **therefore** those in the art have not used it (for that purpose). It is important that this argument is good enough for showing that the PTO did in fact use an unconvincing line of reasoning when stating that the Jordan reference would anticipate our claims. For that purpose the reply was sufficient to remove the claim objection.

Furthermore the PTO (in Response to Argument) also dismissed that the Landen et al., reference that yielded negative result for buspirone for an augmentation strategy with SSRIs, and was not more efficacious than placebo. The PTO argued that that reference concerned treatment-resistant depression and "does not prove it will not work against non-treatment resistant depression, as the very definition of treatment resistant depression [TRD] specifies that it is more difficult to treat then ordinary depression, and not all therapies that are effective against non-treatment resistant depression will work against treatment resistant depression."
The PTO may be unfamiliar with the clinical train of thought at that time. (It was presented before to the PTO with the algorithms on treating depression and TRD that only a single agent was used for non-TRD as initial treatment). Some of the augmentation strategies included either a medication that was known to have adequate antidepressant effect for non-TRD as a stand alone (monotherapy), but giving the two agents together [for TRD] was find to be still working when one was not, or **the art used medications for empirical considerations that did not have an antidepressant effect as a "stand alone" monotherapy**. (The example for this was lithium, thyroid hormone and the negative clinical study for buspirone).
So, if a compound (this case buspirone) was not used for initial treatment for depression (as it was not effective), and was also not find to be effective as an augmentation strategy [for TRD] that is a powerful data and cannot be dismissed. It showed that the agent buspirone simply did not work for any of the depression type TRD or non-TRD, and in turn according to Jordan this non-working agent was showing a receptor profile similar to aripprirazole. So what conclusions can a clinician make based on that? This could simply not anticipate our claims.
This shows that the PTO did not have a convincing line of reasoning that the Jordan reference was enabled for the purpose of our claims and/or it was not convincing that the Jordan reference was anticipating our claims.

> The Jordan reference (page 4) makes also a reference that another agent gepirone (being 5-HT1A partial agonist) (page 4 lines 25-),is **not** quite sharing the same receptor profile as aripriprazole. Note that their test compound was described as having agonistic activity at 5-HT1A receptor (and at page 22 demonstrating high affinity binding to H5-HT1A receptors), and they note that another agent gepirone is being 5-HT1A partial agonist.
> This is in the context that this two compound **not** quite sharing receptor profiles. (Jordan reference (page 4) as above).

The PTO cannot assume anticipation that a clinician (skilled in the art) with either of that above knowledge would go ahead with these uncertainties and give these (experimental) drugs to a patient without sound clinical reason and without undue experimentation.

The fact that aripriprazole was not FDA approved at the time of our priority date shows that the average in the skilled in the art could not use it. That fact again could not be dismissed by the PTO when the PTO sets requirement for enablement that the skilled in the art should be able to use the invention of Jordan (based on the disclosure of that document). That document, with the prior knowledge of the skilled in the art did not place the invention of Jordan at the hand of the skilled in the art.

It is also of note that the Jordan reference did not have any clinical studies.

--

Q&C-(reply)-2): Robertson et al.:
What was said above in particular **under 4c)** is also applicable here for why Robertson could not anticipate our invention. It is also of note that we have amended our claims and cancelled claim 9.

In addition what we referenced with small fonts above is also pertinent showing that the Robertson paper did not have the same patient population of our claims. We have made this clear in our specification:

> Page 2 lines 25 to page 3 lines 10 of our utility:
> Early reports compared the antidepressant efficacy of two older/traditional groups of medications, the tricyclics (TCA) and traditional antipsychotics, or their use in combination, (Robertson, M., et al. 1982; Hollister, 1967). This review by Robertson (Robertson, M.M. et al. 1982) was based mostly on studies with mixed-anxiety depressive states, now more appropriately called as depression with anxiety as a comorbid disorder (Zimmerman, 2002)."

So the risk/benefit ratio is an important for the use of our method, but **the PTO's conclusion to reduce this as the only factor is absolutely incorrect.**

1) As shown above: Robertson paper did not have the same patient population of our claims.
2) The prior art references point to understanding that the antipsychotics (in particular the traditional (older) atypical antipsychotics have depressogenic (depression producing) effect.
3) The prior art expressed doubt of 'true' antidepressant effect of the antipsychotic drugs, or has find a "persistent belief that the antipsychotics are not very effective in the treatment of depression".
4) The risk benefit ratio as disclosed in the prior art (2001) is only one factor considering the other preceding publications. Please note that the said risk benefit was referring to refractory patients (and not to our exclusion criteria, as initial treatment).
5) As we identified under 4c) above there was other consideration that the PTO (and the prior art references) did not take into account.

> Citation from our utility continues:
> "The combination use had been reserved for psychotic depression. A later review summarized the opinion, that "while a 'true' antidepressant effect has been demonstrated for the tricyclic antidepressants, similar effects appear doubtful for the antipsychotic drugs." (Nelson, J.C., 1987).
> The combination use of these medications to treat non-treatment resistant, and non-psychotic depression was never recommended. A book chapter reviewing this topic from year 2001 makes the point that "**the risk/benefit ratio in refractory patients** lacking such features [as near-psychotic rumination or marked psychomotor agitation] generally does not favor [antipsychotic augmentation]". (Price, H. 2001,). The reports available up to date have reserved the combination use of antidepressant-antipsychotics only for psychotic depression, or for treatment-resistant depression.

> From page 1 lines 30-to page 2 lines 1-14 of our utility:
> While chlorpromazine was used early on in the treatment of depression, as tricyclic antidepressants became available the use of antipsychotic medications declined, and they were

never widely used in the treatment of depression in the absence of psychotic symptoms. See also Raskin A. et al 1970, p.170: "There is a persistent belief that these drugs (antipsychotics) are not very effective in the treatment of depression". In general, the use of antipsychotic drugs was reserved for use in patients having psychotic symptoms. It was generally accepted that antipsychotic drugs used alone could not treat major depressive disorder. In fact, it was thought that antipsychotic drugs, including some of the atypical antipsychotics, may even have depressogenic properties. (Harrow, M. et al 1994, Galdi J. 1983, Tollefson, G.D. et al 1998, Maguire, G.A. 2002, Cookson I.B. et al.)
In contrast to antidepressants, antipsychotics alone (including the atypical antipsychotic risperidone) were ineffective in the chronic mild stress (CMS) model (animal simulation of depression) (Papp, M. et al 1996; Papp, M. et al 2000). In sum, many studies showed that antipsychotics do not have significant antidepressant activity and, if anything, may cause a depressogenic effect.

From page 4 from lines 28 / the last paragraph of our utility:
"There have been no reports recommending that the combination therapy can or should be used for a major depressive disorder, or for other depressions as an initial treatment, upon initial presentation to a health care provider (or as soon as possible), or for using the combination as a treatment of first choice, for reducing the risk of suicide."

So the PTO examiners were erring in reducing their conclusions only to one factor (the risk/benefit analysis) and stating that it is a judgment call. There have been many other factors, thus Robertson could not anticipate our invention.

The PTO is also erring in particular and without doubt with stating: "The intended uses recited in the instant claims, for example inhibiting the development of tolerance toward an antidepressant, ... are inherently present in any circumstance where the claimed drugs are administered to a patient suffering form depression..."
The PTO may not be aware but the inhibiting the development of tolerance refers to the antidepressant becoming ineffective. The PTO did not engage into any argument of why this would be inherent. Thus the PTO did not give a convincing reasoning.

The PTO notes that cited documents (**Nelson, Price, or Zimmerman**) did not appear to have been included among the information disclosure statements submitted by Applicant.
All of the references for these documents have been provided to the PTO and had been included and published with the provisional application. Please note that it was the applicant's (former registered patent attorney Deb Anderson and his supervisor Arnold Silverman who made a decision of what references should be included in the information disclosure statements. As I remember, Deb Anderson told me if we include too many references (overwhelming the examiners) that can lead to patent rejection according to some regulation. I can only speculate for the reason for why that happened and have nothing more to disclose. The PTO only noted that said documents were not in the information disclosure statements, but did not request the inclusion of these documents there. If that is desired, please communicate that need with the applicant.
For the benefit of the doubt we list the references again here:

Nelson, J.C. The use of antipsychotic drugs in the treatment of depression. In: Treatment resistant depression. Zohar, J. et al (eds) PMA publishing, New York, 1987.

Price, L.H. et la. Drug combination strategies. 197-222. In: Amsterdam, J. et al (eds). Treatment-resistant mood disorders. Cambridge University Press 2001.

Zimmerman, M., et al: Major depressive disorder and Axis I diagnostic comorbidity. J. Clin. Psychiatry 63:3, 2002; 187-183.

Q&C-(reply)-3): Re: claim rejection over Tollefson et al. '921 (US patent 5958921, of record in previous action, different from Tollefson W099/61027 cited previously) – (olanzapine).
What was said above in particular **under 4c)** is also applicable here for why Tollefson et al. '921 could not anticipate our invention.

Although the PTO makes note stating "Applicant's arguments, submitted July 22, 2009 , have been fully considered and not found to be persuasive to remove the rejection" there was none submitted at that date. The responcse to 5th OA submitted on July 20, 2009 does not contain reference to Tollefson to the applicant's knowledge. The response to the 4th OA submitted on 3-11-09 does (pages 22, 163-166 or till 167). [That also further relates to **Tollefson, WO 99/61027** Combination therapy for treatment refractory depression (priority date May 22 1998 PCT/US99/11276); and **Tollefson, US6,960,5577,** Combination therapy for the refractory depression.]

The "Response to Argument" by the PTO contains some erroneously paraphrased facts and is missing the point the applicant was making:
The PTO stated:
"Applicant argues that Tollefson et al. '921 is not enabled because the depressive patients not diagnosed as psychotic who are referred to in the patent and in the associated clinical trial might possible be actually suffering from unrecognized psychosis." That is not what the applicant said and that is not how the applicant argued.
The PTO continued: "Applicant also *speculates* that no ethics committee would have approved the double-blind study referenced by Tollefson. All of these arguments are *speculation* by Applicant and to not provide any concrete evidence of non-enablement." "An issued US patent is presumed to contain an enabling disclosure for, at the very least, the subject matter of the issued claims..."

The PTO should not brush off the applicants arguments on the basis that an issued US patent is presumed enablement. This phrase by itself does not give assurance **only presumption. Presumption – the word used by the PTO - is not a proof.** (So the PTO did not provide proof that the Tollefson '921 patent would anticipate our claims.) So at minimum the Tollefson's '921 prior art document (if necessary with the other related patent applications and the studies contained therein) should be scrutinized also by the PTO in order to make any judgment as far as the validity of the disclosed study in that patent would or would not really anticipate of the instant claims.

We have given evidence (and we used that word) and not speculation as the PTO rephrased it. We have given evidence based on our observation and collected facts.

We paste our argument herein again:

> **"Tollefson, US 5,958,921** Method for treating depression with olanzapine. (PCT pub WO97/23220) PCT filed December 04, 1996.
> **Based on the following evidence we feel that this Tollefson, (US 5,958,921) reference is misleading or was phrased in a deceptive manner as far as the suggestion for enablement for their broad claims. We could not find any enablement in the Tollefson reference for the purposes of our claims: Since over twelve (12) years of the filing of this application no corresponding publications in professional journals followed this Tollefson patent**

application regarding the use of olanzapine for non-psychotic, non-treatment resistant unipolar, or major depressive disorder, (or for the purposes of our other claims) it is highly doubtful that Tollefson was in the possession of surprising results or the conclusions drawn in our claims. Therefore this Tollefson, (US 5,958,921) reference and ours is clearly different. This is further exemplified below:

As background information we would like to summarize the following: Claim 1, 9, and 12 and dependent claims of this Tollefson, (US 5,958,921) reference which claim a method for treating depressive signs, depression or Major depression not diagnosed with a psychotic condition, without referring that it would be a treatment resistant depression (TRD). They mention without details that the usefulness can be demonstrated by clinical trial, and also mention that such effectiveness was shown in an international double blind trial involving 1,996 subjects randomized 2:1 to either to olanzapine or haloperidol (5 to 20 mg per day) for six weeks, and olanzapine was significantly better then haloperidol wherein the haloperidol treatment group the worsening of depressive signs was demonstrated. (We will comment with our uncovering discovery on this trial below):

Please compare this to Beasely, Tollefson at al Olanzapine versus Placebo and haloperidol. Acute phase results of the North American double-blind olanzapine trial Neuropsychopharmacology 14:111-123 1996

1) While the claims of Tollefson (US 5,958,921) make it clear that their intent was to claim treatment of patients "not diagnosed with a psychotic condition" (claims 1, 9, 12,) this particular application (the 5,958,921 reference) was not presented in a clear and unambiguous way to provide guidance, enablement, or even to know what particular patient population they were talking about. Their alleged enablement – as disclosed by Tollefson – is restricted of demonstration by clinical trial (page 4 5th paragraph on my printout from the PTO web page). There is nothing mentioned if these patients were MDD with TRD, bipolar depression (within the category of depression) or at times patients with schizophrenia or schizoaffective disorder showing depressive symptoms, (but right at the time of their assessment free of psychotic symptoms). If indeed Tollefson representing a major pharmaceutical company would have discovered a surprising new use (pre-requisite for an invention) for MDD, non-psychotic, non-TRD, – specifically with the number of patients referenced in his patent application being almost 2000, a publication in peer-reviewed clinical journals would have followed in over twelve years time. This applicant could not find anything of that nature. The corresponding publications were only for currently known use not conflicting with this applicant's claims. Therefore it is likely – and there is nothing to the contrary in Tollefson's patent application (the 5,958,921 reference), that the patients in the cited study of that patent application are a combination of MDD with TRD, schizophrenia (or schizoaffective disorder) with depression, and bipolar depression. The medical literature search corresponding to that patent application indeed reveals publications in these areas. It also has to be mentioned

as revealed in our application, that both bipolar disorder and TRD are associated with high percentage of psychosis even if the psychosis often goes unrecognized. The language chosen by Tollefson of "a patient not diagnosed with psychotic condition" instead of using non-psychotic patient further reflects or supports that implication (i.e. that psychosis is not excluded, it is just not diagnosed). In summary, this particular application (the 5,958,921 reference) was not presented in a clear and unambiguous way to provide guidance, enablement, or even to know what particular patient population they were talking about. [See also 3) below.] Specifically, and in addition, no enablement was provided for MDD non-TRD, non-psychotic patients, or for he purpose of our other claims.

2) It is also known that other Tollefson (Eli Lilly) reference (e.g.: **Tollefson, WO 99/61027, or US6,960,5577**) had study on MDD with TRD. We have also referenced in our application the Shelton study (2001 Am J Psychiatry) on TRD. Now, it is a concern that the FDA has approved atypical antipsychotics – as monotherapy - for the treatment of bipolar disorder without specific warning that they may not be an equivalent alternative to the traditional mood stabilizers at least in subgroups of patients. It is known, that there is an overlap with psychosis in a high percentage of bipolar disorder patients:
"**About 2/3rd of patients with *bipolar (manic-depressive)* disorder are having a history of at least one psychotic symptom**. Bipolar patients who are psychotic during one episode of affective illness are highly likely to be psychotic during subsequent episodes. [Tsai, SY. M., et al. 2002.])" (page 29 last four lines and page 30 1st line in our provisional application with size 14 copy).
Therefore, in bipolar disorder the antipsychotic monotherapy targeting psychosis, agitation, and anxiety may show a significant difference in the improvement of patients but only as for the group. That does not mean that the atypical antipsychotics can replace the traditional mood stabilizers for all subgroups (and in non-psychotic bipolar patients). Unfortunately the FDA and the clinical marketing did not draw attention to that potentially and likely misleading link. At least a subgroup of the bipolar patients who are withheld from the benefit of the traditional mood stabilizers may suffer, as the above fact/concerns were not mentioned or emphasized by the FDA. **The same may be true for the treatment of TRD**. As we noted in our provisional application (page 35 last 3 lines and page 36 lines 3-4):
"It had been estimated that **a significant proportion, 15% of major depressive episodes fulfill the criteria for psychotic subtype**. (Gumnick, J.F. et al. 2000). ...
...Nierenberg had noted that **in many cases, the cause of treatment-resistant depression may be an unrecognized psychosis.** (Nierenberg. A. A., 1992)."
The Shelton study referenced in our application (2001 Am J Psychiatry) did show only a modest improvement with olanzapine monotherapy for the treatment of TRD, but as is known in a significant percentage of TRD the cause may be the unrecognized psychosis. That may explain the overall difference, and also of why there was only for modest effect for the olanzapine monotherapy for TRD.
We provided enablement in non-TRD through various different mechanisms (as revealed in the reasons part) and also on the interaction of medications,

psychological and [gene expression effect].
The Shelton, the Tolefson (5,958,921, **WO 99/61027, or US6,960,5577** references) **or similar studies on TRD therefore cannot be extrapolated without enablement to non-TRD.**
Therefore these references are clearly different from our claims.

3) Tollefson also disclosed studies on the effect of olanzapine on "anxious and depressive symptoms accompanying schizophrenia". (Tollefson GD et al A double-blind, controlled comparison of the novel antipsychotic olanzapine versus haloperidol or placebo on anxious and depressive symptoms accompanying schizophrenia. Biol Psychiatry 1998; 43: 803-810.) In that study, Tollefson specifically stated that "anxiety and or depression may persist in the absence of overt psychosis" [in the schizophrenic patients]. (page 806 second column under discussion, line 5-7). Whether their patients disclosed in their study referred to in their 5,958,921 application as "not diagnosed with psychosis" included that patient population is unknown, thus the 5,958,921 reference was not presented in a clear and unambiguous way. If fact based on the presented evidence here we feel that it is misleading, as further evidenced next:

4) In the 5,958,921 reference Tollefson refers to their international double-blind study involving almost 2000 subjects randomized to receiving either olanzapine or haloperidol for 6 weeks. It is respectfully submitted that

in order to conduct such a large scale study usually smaller non-double blind study is conducted and revealed. (We have not found such a study in the literature for MDD non-TRD, non-psychotic).

It had been known in the literature (as it was also disclosed by the applicant) that haloperidol can cause depression. In fact Tollefson was also revealing that finding.

With all that and with the knowledge of the art at the time of Tollefson's application it is respectfully submitted that no ethics (research) committee would have approved such a large scale study on unipolar depression or MDD with non-psychotic and non-TRD, and from the definition of unipolar depression on non-bipolar patients. They would not allow a known depressogenic agent the neuroleptic haloperidol (causing depression as revealed in the literature and also in our utility) to be used in the control group of one third of the 2000 patients, also because of the serious and potentially deadly side effects like tardive diskinesia (TD) and neuroleptic malignant syndrome (NMS). Also the neuroleptic haloperidol is known to cause akathisia (restlessness) that is linked of causing suicide. (see e.g. Drake R.E. Suicide attempts associated with akathisia. Am J. Psychiatry 142:4, pp 499-501, April 1985). **Therefore even tough the broad claims of the Tollefson reference covers unipolar depression or MDD with non-psychotic and non-TRD, it is quite convincing with absolute certainty that the patients in his study were not consisting of such - and based on the evidence we believe falsely claimed patients.**

In addition claiming an antidepressant effect (for non-psychotic patients) in that Tollefson US 5,958,921 reference in comparison to a drug that is known to cause depression is a non-convincing rational. If you give a drug that is known to cause depression (haloperidol) and compare this with placebo and the

placebo group would show a better mood that would not make the placebo an antidepressant.

As regards to patients with schizophrenia Tollefson has revealed that "the literature generally reflects that given an adequate dose and time interval for a positive symptom response to conventional antipsychotic drugs, some mood improvement will be seen". Pages 806 second column under discussion lines 18-21. (Tollefson GD et al A double-blind, controlled comparison of the novel antipsychotic olanzapine versus haloperidol or placebo on anxious and depressive symptoms accompanying schizophrenia. Biol Psychiatry 1998; 43: 803-810.) Therefore **no** generalization can be made of the "antidepressant" effect of antipsychotics for MDD non-TRD, non-psychotic patients.

5) In the 5,958,921 reference Tollefson makes mention of his intention of using the term "treating" including profilaxis, but no enablement for how that would be achieved, or proven by clinical trials were presented as far as the purposes of our claims.

In summary, the 5,958,921 Tollefson reference is not a clear and unambiguous disclosure or we feel based on the above it is even a misleading or deceptive, and no evidence was presented for enablement as regards to our invention. Therefore the two applications are clearly different.

Therefore, this document does not foresee our claims, (it is not enabling, has insufficient disclosure; it fails to put the subject matter of our claims within the possession of the public, that is someone with general skills in the field could have not used the referenced document with their own knowledge to make our claimed invention themselves; so it does not affect the novelty of our application."

Please note that for patentability and for non-obviousness an "unusual and surprising results" was considered as for filling that criteria (as disclosed by an influential court). The PTO cannot disregard the fact that **if** indeed the Tollefson reference would have had over 1000 patients treated with non-psychotic major depressive disorder (and non-bipolar, non-treatment resistant) in a double bind study, then this **"unusual and surprising results"** would have been published in professional publication **in 14 years**! However, it was not published, no such publication exists in the professional literature. (If the PTO does not believe me he may unsuccessfully search for it at the "pub med" US government webpage). This is evidence and not speculation. This is particularly true when the authors use a language that "in one particular study" and giving no reference to the "other" study.

The PTO also dismissed the arguments made by the applicant saying that: "Applicant also speculates that no ethics committee would have approved the double-blind study referenced by Tollefson."

This is not a speculation but is based on the applicant's experience (and the applicant had been Board Certified in Psychiatry when he submitted his patent applications). When conducting studies, the ethics committee looks for some prior evidence, convincing rational and support that it would be likely that the double bind study would provide a

benefit (and no harm to the control group). The ethics committee would not have (could not have) approve a study involving about 2000 people without prior proof, case studies and/or adequate disclosure (for the diagnostic group of non-psychotic, non-TRD unipolar depression). Where was that disclosure provided in that patent application (or in prior art professional publications)? It was not there. It would have been the interest of the drug company (and their duty) to provide all that information to the PTO and the skilled in the art in exchange of a patent.

In addition the PTO is dismissing that the same authors (Tollefson) did publish in a professional publication that he had knowledge that haloperidol (older type antipsychotics) would and could cause depression. (Note that haloperidol was compared with olanzapine in the Tollefson study to compare antidepressant effect). See our Utility: page 2 lines 6-9: In fact, it was thought that antipsychotic drugs, including some of the atypical antipsychotics, may even have depressogenic properties. (Harrow, M. et al **1994**, Galdi J. **1983,** Tollefson, G.D. et al 1998, Maguire, G.A. 2002, Cookson I.B. et al.)
So the research study in comparing "anything" (any substance that does not cause depression) to a compound that would cause depression would find that the "anything" (even inner substance, sugar pill/placebo) is better for "treating" depression then the one that is causing it. This is not speculation but clearly presented fact at least in regards to that that research design and Tollefson '921 could absolutely not anticipate our claims.
So yes, the ethics committee could not approve such a study of exposing about 1000 people (the control group) to a known depressogenic agent. The ethics committee could only approve that study (to give a traditional antipsychotic to 1000 "control" patients if the patients had prior diagnosis of longstanding psychotic illness (or bipolar disorder) [and therefore it was standard (and acceptable) to give them haloperidol]. If they had these diagnosis before they could not have had the diagnosis of major depressive disorder. But this (about the ethics committee) is only in a small print (and secondary) to the argument about the research design that cannot be used because it is faulty in it's design.

In summary the Tollefson '921 also did not anticipate our claims, and the claim rejection must be withdrawn.

--

The PTO has cited the Wands factors *and Genetech,* 108 F.3d at 1366, that sates that, *"a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."*

We cannot agree more and we emphasize here the underlined parts!

It is in particular revealing when the applicant's invention is compared to Chappell and the other cited references that has only vague (that is very vague) generalized hints on the combination being useful for depression (in vague and general term) or for all mental disorders, all neuropsychiatric disorders without any explanation whatsoever [and without taking into considerations the other factors we discussed under 4) and 4c)] – and yet the PTO declared these prior art documents "enabled". In fact as we showed if anything these documents were the ones with "vague intimations of general ideas that may or may not be workable". - In contrast, the applicant had full disclosure, an extended guidance that put the invention to the hand of the skilled in the art without undue burden, had enablement for the method (based on his conclusions the applicant collected and drawn from many data that was collected and correctly interpreted from prior art), and the applicant also had drawn conclusions overcoming the barriers and previously unsolvable problems by others stating a new path rather then following a trail, disclosing reasons that would overcome the strong teaching against and the divergent guidelines. So according to Wands factors *and Genetech,* 108 F.3d at 1366, that sates *patent is... a compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention"...[and it does not say it needs an experiment].* The applicant has achieved these goals.

Line by line reply:

The applicant would like to start his reply to the OA's page 43 Further Comments first as in the context (and lack of specific answers to the arguments raised by the applicant) this seems to be the most sensible.

We would follow similar formatting as in the line by line reply to the prior office actions. For better organization, we put our brief reply in tables. Indented to the left or left column is the copy of the 6th office action's pertinent part, indented to right or right column is reference or our brief reply to the 6th office action (incorporating/referring to the above replies).
Please also refer back to our comments made before the line by line reply (so that we can avoid unnecessary repetition).

Further Comments **Difficulties in Argument and Claim Construction** (p43) As mentioned at the beginning of the office action, *lack of knowledge of patent prosecution* is usually a hindrance to prosecuting a patent. This is *seen in the increasing number of claims* in the application,	The examiner is describing that he is aware that the applicant would need help (implied also need help from the examiner) in proper prosecution of the patent. It had been described before of how the applicant lost his attorney representation (being fired as he chose to reply in details providing evidence). It is the applicant's understanding that it is the PTO who regulates/credentials (and conducts the examination) for patent attorneys. As it was said before the undergraduate field of the patent attorneys are not listed under the PTO web page. Any qualifying attorney with expertise in the field of pharmacology and our field would likely to have conflict of interest as he or she would not be able to survive serving only small entity inventors (as there are not too many in that area). So that puts an increased expectation on the PTO to provide assistance to this applicant as to a small entity inventor not represented by attorneys. Some of the early claim amendments were done by patent attorney (possibly outsourced). As the applicant has gained more knowledge over time on crafting the claims, he too realized that the claims could have been simplified to a lesser number of claims. The applicant made this modification at least in his Mexican application. Now, most importantly, it should be mentioned that the applicant have requested claim drafting assistance not only in general, (but also very specifically when the applicant was crafting alternate claims and was asking the examiner to make comment on it). However, the examiner ignored these questions and thus the applicant needed to incorporate these new claims in the next reply in order to get an answer from the examiner. So yes, the number of claims could have been reduced if the examiner would have been answering

and the *confusing, disorganized nature of Applicant's responses, which have grown to over 200 pages in length*, and which do not properly address the actual issues on which the patentability of the claims depends.	the applicant question, and complying with claim drafting assistance – at least to the degree of making an effort of noticing the applicant question(s). The applicant had the same sense on the examiner's response. The repetitious nature of the examiner's response might have been originated that these comments by the PTO had to be tailored to various patent rules, but the same argument by the examiner was pasted again and again in the replies, which – in the applicant's eye – made the OA choppy and disorganized. Since the applicant had to tailor his response to the appropriate section of the OA, the organization (or disorganization) just followed the structure of the OA awaiting for a reply.
While Applicant is entitled to have any set of properly drafted claims examined on the merits, the manner in which Applicant has prosecuted this application makes it difficult to adequately consider and reply to every argument. Furthermore, Applicant demonstrates a lack of understanding of the standards of patentability and claim interpretation that guide the process of patent examination. Further explanation is given herein in the interest of expediting prosecution of this application.	The reason why the applicant has chosen to provide the reply in a "line by line reply" was to tailor his reasoning to the OA's appropriate part. It is also noteworthy that the applicant operates (mainly) from clinical standpoint, while the examiner is not a clinician (and did not even seem to comprehend some clinical principles) and seemed to focus on his understanding of the art by organizing his reply according to the patent rules. When clarifications were needed for the applicant (or for the evaluation process) and when the applicant was citing patent rules (from self-help books) of why the rejection had to be withdrawn, these rules were pretty much systematically ignored by the examiners deepening the communication gap. The applicant has clearly pointed out his reasoning, many of which were ignored by the PTO. This very reasoning that were ignored by the PTO in many instances necessitated to bring these reasoning up again and again in the next reply and summarize at least some of them in the last reply. So this is why the last reply was over 200 pages. The content of the last reply by

In response to Applicant's request for assistance in drafting allowable claims, the examiner does not see any allowable subject matter contained in the disclosure. Therefore it is not possible to draft allowable claims.	the applicant was aiming to help the PTO and the application process of **repeating pertinent parts not previously answered by the PTO.** Unfortunately, in this final OA the PTO again disregarded many of our reasoning, and made only general comments (and formed opinions). It is difficult to accept an OA if it seems to avoid a rational reply to a logical argument, or if it basically states that they do not have to reply (or take this reasoning into consideration). The other approved patents – also raising the question of discrimination – were bought up in part to point out the unconvincing reasoning in our examiners' logic thus being an argument necessitating the withdrawal of claim rejections. The fact that many of the applicant's reasoning were disregarded was frustrating to the applicant and did not seem to him he got proper attention to his arguments from the PTO.

Claim interpretation (p44) Each claim is interpreted on its own merits. Claims are only limited by the specification or other aspects of the disclosure when the disclosure explicitly defines a term appearing in the claim, or when the claim uses specific "means-plus-function" language as described in 35 USC 112, sixth paragraph. In all other cases, claim are given their broadest reasonable interpretation consistent with the prior art.	
For example a "method for treatment of a non-psychotic patient having cognitive distortions" as described in instant claim 3, encompasses any method wherein the claimed therapeutic agents (the antidepressant and antipsychotic) are administered to a patient having cognitive distortions. The scope of the claims are not limited only to what is discussed in the specification unless the specification	In our previous replies (e.g. reply to the 3rd OA page 18-) we have addressed our answer that included of <u>why the anxiety and cognitive distortions are not synonymous</u>. However, to further elaborate on this issue (and asking for clarification) the following should be noted: It is known that the treatment of anxiety (depression, or any mental illness) extends life. The data is

clearly defines a particular term in a particular manner. Therefore, although the specification describes cognitive distortions in the context of thought patterns that reinforce depression and complicate its treatment, other sorts of cognitive distortions, such as those occurring in patients suffering from anxiety disorders (e.g. overestimating risk, focusing on negative outcomes, overestimating the possibility of negative outcomes) also fall within the objective scope of the claims. Similarly, a phrase such as "as soon as possible" can be interpreted in many different ways, and therefore does not serve to significantly limit the scope of the claims.	there that mental illness shortens life span (not only because of suicide, but because of cardiovascular complications). So, let's suppose that somebody would have a claim of by treating anxiety with a (broad class description of a structure find in the anti-anxiety agent) through which that method would extend life (for that population) without the actual knowledge of how that life extension occurs (other then empirical data). Would that claim exclude another patent being issued when the other invention is targeting a different mode of action let's say genetic manipulation and it would happen that very specific structure described in the above patent (but without the anti-anxiety effect) would be responsible for an epigenetic change and therefore the extension of life for all people? The mechanism of action is different! Constructing a house involves many different construction materials walls (from brick and plaster and wood) roof (that can be concrete or other materials. Cognitive distortion is at most one aspect of anxiety and many of the pharmacological methods (like benzodiazepines) (as we have specifically described in our prior replies) do not target the cognitive distortion but other receptors. No prior art said that the combination of antidepressants and antipsychotic would target anxiety, no prior art enabled such a statement. So why would our claims be precluded from patentability. Why would be our claims (in regards to cognitive distortion and smoking) be not allowable? Maybe it would be helpful if the PTO would explain of how come so many other patents (that we listed) were all issued for smoking cessation. My former patent attorney (Deb Anderson) could not explain that to me. This may shed a light for the applicant, if the objection is maintained.

	(Again the applicant is not asking an issuance of a patent just because the PTO erred in other cases, but would like to exercise his right to know!) Cognitive distortions (to some degree) also occurs in normal people. Clinically problem is considered only when it causes functional impairment. The PTO is also erring in dismissing the applicant's prior reply in saying that his analogy that anxiety (without cognitive distortion) also occurs in normal people exposed to (extreme) stress – and the PTO is saying that if that extreme stress is caused by a totalitarian regime, or abusive boss that does not manifest in pathological illness (disease) like what the "cited prior art" is talking about. The PTO again shows unfamiliarity of the exact description of this applicant (e.g. on the Stanford prison experiment) that even an "as if" experiment or situation can elicit the exact same clinical and biological changes (that we observe in the [mental] disorder) and yes, normal people will become symptomatic the same way as the ones where genetic predisposition or other causes led to the anxiety disorder or to the depression. So the PTO examiners again are forming their opinion in disregarding the facts and the submitted disclosures from the applicant. At another place the PTO again incorrectly equals OCD (obsessive compulsive disorder) with cognitive distortion when that is just not the case.
Furthermore once the broadest reasonable interpretation of the claims is determined, the claim must be allowable over its entire scope to be allowable. That is, if the prior art anticipates or renders obvious any one embodiment of a claim, then the entire claim is anticipated or obvious. Similarly, for a reference to render a claim obvious, all that is necessary is that at least	Should not be the PTO's job – as defined by law – to help this applicant with claim drafting assistance and draw attention what part(s) of the claim(s) should be deleted in order for allowance for an issued patent? This is requested along with specifics not just reciting patent principles in general.

one obvious modification of the reference falls within the boundaries of the claim. For example, even if the prior art such as Chappell et al. teaches a number of different D4 antagonists, of which only one (olanzapine) falls within the claim limitations, that single embodiment can render the claim obvious even if the broad recitation (D4 antagonists) is not coextensive with the scope of agents (e.g. atypical antipsychotics) used in the claims.	(This part about D4 was discussed above).

Previous issued Patents (p45) Applicant has repeatedly accused the Office of discriminating against small entities in favor of large drug manufacturers, pointing to various patents issued to drug companies	The applicant objects to the wording of the PTO. The applicant never accused the PTO for discriminating against him (that could be said only if he would have gone to court), but the applicant did raise the issue of discrimination (and in doing that he pointed to facts that needed to be clarified). The PTO refused (and is continuing to refuse) dealing with the examples of the other (issued patents) that not only is raising an issue of discrimination, but also is pointing that the examiners could not have a convincing reasoning. (If their reasoning would be convincing the other patent(s) should have not been issued either. That is very relevant to the examination process, and cannot (and should not) be brushed off.
which allegedly should set a precedent that would lead to the allowance of the present claims. Firstly, the allowance of a patent does not set precedent. Examiners are bound by the Constitution, the Patent Act, the Manual of Patent Examining Procedure, and decisions by the Board of Patent Appeals and Interferences and the Federal courts. They are not bound by the decisions of other examiners in other applications, because the prosecution of each case is an independent process which depends on the specific fact pattern of the	As said before, the applicant never asked to get his patent issued just because the PTO erred in other instances. However, it would be diligent for the PTO to acknowledge a mistake, and if the mistakes are in such an enormous numbers as the list of the other patents that was brought up, that would be of great concern. The applicant wants to exercise his right to know! If there is such a gap between the examiners and the applicant in the communication, it would be expected that the PTO would make every effort to bridge

case. The mere citation of an issued claim in another application is not in itself an argument for the patentability of a similar claim in the present application without knowledge of the thought process that went into the allowance of said claim.	that gap, and not to ignore or brush of the applicant's arguments, the presented facts (e.g. secondary considerations/factors; cited relevant references [e.g.4c)], or even referenced other patents.

Applicant's Double Standard Regarding His Own and Others' Work (p46) Applicant has repeatedly made the argument that others' publications and patent applications are not available as prior art against the present claims because they are non-enabling due to uncertainty or contrary teachings in the art, or due to regulatory and legal standards that would consider the methods taught in the prior art to be malpractice as they violate current clinical guidelines. These arguments are made despite the fact that all of the concerns raised by Applicant could be equally applied to his own claims. Applicant's disclosure does not introduce any new evidence or teachings over the prior art. The disclosure consists merely of a summary of the prior art uses of antidepressants and antipsychotics for treating depression and resisting suicide, and the suggestion that more aggressive treatment with the combination of these two drugs would yield a clinical benefit in a reduced risk of suicide. Applicant's disclosure does not provide any new facts regarding antidepressant or antipsychotic therapy. It does not show any new benefit for this combination, but merely theorizes	This have been addressed above, that the applicant did not have double standards. The concerns cannot equally apply to the applicant's own claims if he made a new disclosure (previously not recognized by others), if he enabled the skilled in the art of how to overcome the obstacles set by divergent guidelines and strong teaching against the method. So the PTO is either does not understands the clinical aspects of the method they are evaluating, or they did not read it or did not read it carefully enough) to maintain such a distorted statement. (This had been sufficiently discussed above prior to the line-by-line reply).

that treating cognitive distortions secondary to depression using an antipsychotic would improve the treatment of depression, and reduce the likelihood of the patient committing suicide before the antidepressant has time to work. These arguments in the disclosure reflect Applicant's judgment as one skilled in the art regarding off-label administration of antipsychotic drugs, which is in fact a routine aspect of the current state of the art for treatment of psychiatric disorders. It is the case that those skilled in the art will prescribe antipsychotics off-label when they believe doing so is warranted, for example for treatment resistant depression. Applicant claims in his arguments that prescribing these drugs for non-treatment-resistant depression is malpractice and not enabled by the art. However, he also asserts that he is enabled for practicing the same method because of the new discovery disclosed in his application. This new discovery amounts to his personal judgment that the benefits of antipsychotics for augmenting antidepressant therapy are worth the risks. This is the same judgment used by any clinician prescribing a drug off-label, and if Applicant's judgment is sufficient to enable this off-label use, <u>than the judgment of other clinicians in the prior art who suggest the combination of an antidepressant and an antipsychotic for initial treatment of depression is equally valid.</u>	(When did the prior art show any evidence that the skilled in the art was in possession of overcoming the barriers (strong teaching against, divergent clinical guidelines), when did the prior art show any evidence of the practice of the method of this invention?) The same line of reasoning can be made then to any invention, that it was reduced only to the judgment of the skilled in the art of not building and using the invention that otherwise they could have.
This pattern of argument is most striking as regards the enablement of treatments using ketamine. Applicant's specification provides no significant disclosure of ketamine as an antidepressant. The only	I do not know what is striking about this, as ketamine was disclosed to have antidepressant effect. It is a different enablement requirement to be able to use

teaching regarding ketamine is its inclusion in a laundry list of antidepressants on p. 12 line 20 of the specification. In reciting ketamine in this manner, Applicant is relying for enablement on the fact that it is known in the prior art as an antidepressant, but relying for non-obviousness on the claim that one of ordinary skill in the art would not be able to use ketamine as an antidepressant. If ketamine were not known to have antidepressant properties in the prior art, its mere recitation in this manner would not be enabling. However, in response to the Berman et al. reference, Applicant argues that the hallucinatory and anesthetic effects of ketamine would prevent one of ordinary skill in the art from using it in place of other antidepressants disclosed in the prior art. (see p. 79 of Applicant's response filed 8/27/2007) If this were the case, then Applicant would also lack enablement for using ketamine as an antidepressant in the claimed methods, since he is basing his case for using it on exactly the same prior art teaching that are accessible to everyone else.	ketamine as initial treatment in combination with antipsychotics (for the reduction of suicide). The PTO also disregards considerations mentioned under 4) and 4c).
Standards of Patentability (p48) Applicant's responses indicate a misunderstanding of the standards of patentability. 35 USC 102 states: The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention. In other words, in order to be enabling, a patent disclosure must enable one skilled in the art to practice the invention.	When did the Chappell, Faour and other references (with their broad description as broad at times as "for all mental illnesses", "for all neuropsychiatric disorders") disclose how the skilled in the art should overcome barriers of strong teaching against, divergent clinical guidelines? When did these prior art documents consider what we described under 4) and 4c)? If they did not why is the PTO insists that these were enabled? When did these documents make even a mention on the paradoxical effect of the antidepressants causing suicide? If they did not, how would that enable the skilled in the art to practice

	that allegedly enabled invention? Why does the PTO disregard the secondary factors showing that one skilled in the art was not using the invention and in particular about the FDA directors perplexing about their inability to solve a problem of the antidepressants causing paradoxical effect and suicide?
This is a separate requirement from the standards used by federal agencies regulating the use of certain inventions, such as the Food and Drug Administration, and is also distinct from the legal and ethical standards governing medical practice, and the standards used by peer-reviewed publications in the acceptance of articles for publication. There is no requirement that the invention be shown to be superior to the current state of the art, as is the case for FDA approval and avoidance of malpractice lawsuits. <u>The only requirement is that the application place the public in possession of the invention, in exchange for exclusive patent rights to the invention for the patent term.</u> Inventions which are immoral or illegal, or which are not commercially viable, for example, can still be patented. Patents to drugs which have never been approved by the FDA, or whose use has been discontinued due to safety concerns, are still valid patents and enabling for the purpose of anticipation or obviousness. For example, the non-steroidal antiinflammatory drugs rofecoxib (Vioxx®) or valdecoxib (Bextra®) have been withdrawn from the market because of adverse effects. In view of what is known about these drugs, administering them to a patient would constitute malpractice. However, if an applicant were to file a patent application claiming these compounds or their use as non-steroidal antiinflammatory agents, the patent would be rejected under 35 USC 102 and/or 103 as anticipated and/or obvious over prior art publications describing therapy with these	We have addressed this above. (As shown above prior art failed to place the invention in the possession in the public). This was very specifically addressed above before the line-by-line reply.

drugs, even though no one actually practices the methods described in the prior art at the present time due to safety and malpractice concerns. In the instant case, a similar situation applies. Combinations of antidepressants and antipsychotics are known in the art but are not currently used in clinical practice as first-line therapy for depression because of concern over adverse effects, just as valdecoxib and rofecoxib are known to have non-steroidal antiinflammatory activity but are not used in clinical practice because of side effects. Publications exist (Howard et al., Chappell et al., Pivac et al.) describing using antidepressant/antipsychotic compositions.	As we mentioned under 4c) it is not just because of the side effects).
In order for a reference to be non-enabling, there must be a clear teaching in the art casting doubt on whether or not one skilled in the art would be able to practice it, not merely evidence that one skilled in the art would decide not to practice it.	This was very specifically addressed above before the line-by-line reply.
The question of whether or not to use antipsychotics as first-line treatment for depression is one of prudential judgment.	**The following is important:** The PTO cannot reduce this complex issue (when many considerations should be dealt with) to a simple judgment.
For example, is the suffering of untreated depression more or less tolerable than the suffering caused by extrapyramidal side effects?	**The PTO examiners are not clinicians and this is evident of them raising this sets of questions.** Extrapyramidal side effects – if recognized or anticipated – can be dealt with in many different ways. You can give medications to counteract side effect or chose one with minimal risk to that. So the answer is evident to a clinician. The discussion with a patient also means that you do involve the patient in the decision making.
Is a patient more likely to commit suicide due to untreated depression or due to drug-induced akathisia?	The answer to that is also evident if the examiners would have carefully read the application and would be aware of the available statistics. Drug-induced akathisia was brought up in the prior art (for the SSRIs), and in particular the older type

	(typical) antipsychotics may also have that side effect. This side effect is not typical for the newer class atypical antipsychotics and dopamine system stabilizers (in our best mode). However, there are strategies to deal with and/or manage akathisia if and when it occurs.
Is a death from suicide more or less of a tragedy than a death from neuroleptic malignant syndrome?	Again the answer to that is also evident if the examiners would have carefully read the application and would be aware of the available statistics. The examiners are not familiar with neuroleptic malignant syndrome and did not encountered that. This is a rare condition, (but the applicant had seen several, and all were caught early and treated, so no death occurred). So the answer is evident to a clinician.
Is it morally preferable to take action that puts another's life in danger, or to refrain from action that could save their life?	The PTO again did not read the application in its entirely and is unfamiliar with the topics we discussed in our specification otherwise the examiners would have not ask this question. This is why we went in length explaining the "for the benefit of the group". That, along with a discussion with a patient should determine the best action. So the answer should be evident to a clinician, after reading our enablement.
These are questions that cannot necessarily be answered by the teachings of the prior art. The decision of whether or not to use these drugs in this manner is not a settled scientific question which could render the prior art non-enabling, but simply the judgment of the majority of those skilled in the art, which has been codified in a set of guidelines.	The PTO has shown the unfamiliarity with the art by raising the above questions and is also erring in his conclusions. The problem is that the PTO is also using these erroneous conclusions and unconvincing line of reasoning to "support" claim rejection.

Evidence of Secondary Considerations (p51) Where an application claims an invention that is prima facie obvious over the prior art, but discloses new considerations that	This was very specifically addressed above before the line-by-line reply.

differentiate it from the prior art, the prima facie obviousness can be overcome and the invention patented. In order to prove a case of secondary considerations, the case must be supported with evidence that the present claims are somehow distinct from the prior art. For example, evidence that practicing the claimed invention produces an unexpected benefit not seen in the prior art. Regarding evidence of unexpected results, according to MPEP 2145, "A showing of unexpected results must be based on evidence, not argument or speculation. In re Mayne, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997)" Applicant's disclosure presents no concrete data that the invention practiced as claimed (i.e. administering a combination of an antidepressant and an antipsychotic agent as first-line therapy for depression) produces any unexpected results. (e.g. reduced risk of suicide or suicidal thoughts) Evidence may be present in the specification as originally filed or introduced in a declaration under 37 CFR 1.132. Regarding Applicant's arguments considering the need in the prior art for a solution to the paradoxical effect of antidepressants causing suicide, and the alleged failure of the art to propose a solution, the reference **Reeves** et al. (Included with PTO-1449) discloses a solution to this problem, through risperidone augmentation of antidepressant therapy. Unlike Applicant's unsupported speculation, the authors of this publication provide actual evidence that the combination of risperidone and various antidepressants reduces suicidal ideation compared to the combination of an antidepressant and placebo. Therefore the prior art has in fact produced a solution to the problem of suicidality in patients taking antidepressants. Therefore others in the art have not failed to solve the problem that	Error made by the examiners: (For emphasis we repeat parts of what was already said above before the line-by-line reply): While Reeves reference from 2008 (that we disclosed to the PTO) does show an effect of the combination reducing the risk of suicide, it does not talk about nor does it mention paradoxical effects of antidepressants (or their method reversing that effect). Reeves publication from 2008 is not a prior art and cannot be cited as such. Therefore the PTO erred in making these statements and in rejecting our claims.

Applicant identifies. More generally, evidence of secondary factors must include actual evidence that the claimed invention might solve the problems identified in the art, or succeed where others have failed. Applicant gives no basis in his disclosure for believing that his speculative line of reasoning would succeed where the art has failed to find a solution to the problem of suicidal ideation. More generally, patent protection is granted in exchange for disclosure to the public of a novel, useful invention, not an unsupported idea. Many people can have a good idea but never reduce it to practice. A patent is granted to those who did the hard work and novel experimentation necessary to put the invention into practice. It is not granted for a mere speculation or suggestion to modify the prior art in a particular manner. While the disclosures of patent applications, including Applicant's own disclosure are given the benefit of the doubt as regards the enablement of the subject matter they describe, a higher standard is required when alleging secondary considerations. Applicant's disclosure does not meet those standards and cannot support secondary considerations to overcome a case of prima facie obviousness.	

Conclusion (p53) No claims are allowed in this application. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action. This action is a final rejection and is intended to close the	The applicant for claims 1 and 2 did not have an amendment and the PTO still communicated an new objection for the first time (the "as soon as possible" wording). So the final rejection *may* be improper. Clarification to that is requested.

prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below. If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims Conclusion No claims are allowed in this application. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action. This action is a final rejection and is intended to close the prosecution of this application. Applicant's reply under 37 CFR 1.113 to this action is limited either to an appeal to the Board of Patent Appeals and Interferences or to an amendment complying with the requirements set forth below. If applicant should desire to appeal any rejection made by the examiner, a Notice of Appeal must be filed within the period for reply identifying the rejected claim or claims appealed. The Notice of Appeal must be accompanied by the required appeal fee of $250.00. If applicant should desire to file an amendment, entry of a proposed amendment after final rejection cannot be made as a matter of right unless it merely cancels claims or complies with a formal requirement made earlier. Amendments touching the merits of the application which otherwise might not be proper may be admitted upon a showing a good and sufficient reasons why they are necessary and why they were not presented earlier. A reply under 37 CFR 1.113 to a final rejection must include the appeal from, or cancellation of, each rejected claim. The filing of an amendment after final rejection, whether or not it is entered, does not stop the running of the statutory period for reply to the final rejection unless the examiner holds the claims to be in condition for allowance. Accordingly, if a Notice of Appeal has not been filed properly within the period for reply, or any extension of this period obtained under either 37 CFR 1.136(a) or (b), the application will become abandoned.	On February 19, 2010 the US PTO Inventor Assistance Center [ref# 1-163400515] has brought to my attention that there is another option that the inventor has and that is to submit again an RCE (request for continuing examination). (The Center also identified that – if the applicant feels it is warranted, a Continuation in part can be filed at any time the patent is still pending – that [as implied] may be useful for overcoming "new matter" objections). The examiner therefore did not give a full disclosure of the applicant's rights. PTO regulations (MPEP, Section 707.07 (j)) specifically require patent examiners to help inventors in pro se (no lawyer) cases.

Now let's go back to page 2 of the OA.
(Most of these had been sufficiently discussed above prior to the line-by-line reply).

Detailed Action	

This office action is a response to applicant's communication submitted July 22, 2009 in which claims 53, 84, 130, and 140-143 are amended and new claims 144-147 are introduced. This application claims benefit of provisional application 60/319436, filed July 30, 2002. Claims 1-38, 41-43, and 48-143 are pending in this application. Claims 1-38, 41-43, and 48-143 as amended are examined on the merits herein.	
Applicant's most recent response contains numerous insults and hyperbole directed at the examiner, comparing the examiner to a conman, a psychopath, or a child abuser, and accusing the examiner of using pseudologic, discriminating against the applicant, victimizing the applicant, and subjecting the applicant to stress that is compared to battery, murder, or attempted murder, and which is described, in apparent seriousness, as a criminal act. According to 37 CFR 1.3, "Applicants and their attorneys or agents are required to conduct their business with the United States Patent and Trademark Office with decorum and courtesy. Papers presented in violation of this requirement will be submitted to the Director and will not be entered. A notice of the non-entry of the paper will be provided. *Complaints against examiners and other employees must be made in correspondence separate from other papers.*" While the present response has been considered as is, Applicant is requested to abide by standards of decorum and courtesy in further communications with the office. Again, Applicant is reminded: An examination of this application reveals that applicant is unfamiliar with patent prosecution procedure. While an inventor may prosecute the application, lack of skill in this field usually acts as a liability in affording the maximum protection for the	The applicant objects to the re-phrasing his petition to the Commissioner of Patents as insults directed at the examiner(s). The applicant considers himself a well trained psychiatrist, and as such it is standard in his practice (when he deals with patients) to document behaviors objectively and not use so called "labeling" that is a "no-no" in the field. So the applicant (even in non-patient setting) paid special attention of phrasing his observations objectively, and in a way of staying within the boundary set by his profession (for example using the language often used in psychological tests – and still avoid "labeling"). The applicant presented factual observations (including specific data pointing to the fact that the examiner(s) have not even read his application and submitted materials in full. (The facts still point to that direction even if the examiner insists otherwise). The applicant's objective was to get resolution to his complaints, to get acknowledgement to his questions, and to point to the seriousness of the matter (and not to insult anybody).As I remember, the petition even contained an apology – even though the applicant viewed himself in the position of a victim. The complaints have been made (and addressed to) in a petition to the Commissioner of Patents.

invention disclosed. Applicant is advised to secure the services of a registered patent attorney or agent to prosecute the application, since the value of a patent is largely dependent upon skilled preparation and prosecution. The Office cannot aid in selecting an attorney or agent. A listing of registered patent attorneys and agents is available on the USPTO Internet web site http://www.uspto.gov in the Site Index under "Attorney and Agent Roster." Applicants may also obtain a list of registered patent attorneys and agents located in their area by writing to the Mail Stop OED, Director of the U. S. Patent and Trademark Office, PO Box 1450, Alexandria, VA 22313-1450 Applicant's amendment, submitted July 22, 2009, with respect to the objection to claims 6, 9, 10, 12,114-35, 37, 41-43, 48, 49, 51-56, 58-94, 96-107, 109-121, and 124129 for containing underlining and strikethroughs in text that has not actually been inserted or deleted in the most recent amendment, has been fully considered and found to be persuasive to remove the objection as the claims are currently listed without the extraneous underlining and strikethroughs. Therefore the rejection is withdrawn. Applicant's amendment, submitted July 22, 2009, with respect to the rejection of instant claims 140, 141, and 143 under 35 USC 112, second paragraph, for being incomprehensible, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to clearly indicate a therapeutic method involving additional steps wherein certain therapeutic considerations are discussed with the patient. Therefore the rejection is withdrawn. Applicant's arguments, submitted July 22, 2009, with respect to the rejection of claims 127 and 128 under 35 USC 102(b) for being anticipated by Robertson et al., have been fully considered and found to be persuasive to remove the rejection as these claims are seen to specifically require that the antipsychotic be an atypical antipsychotic or dopamine system stabilizer, and furthermore the mention of sulpride, an atypical antipsychotic, in the reference is not seen to involve administration to patients having cognitive distortions. Therefore the rejection is withdrawn.	This topic had been discussed in prior replies, and the applicant again feels that his comments were not acknowledged (or read) in this regards. (That included the difficulty of finding a qualified patent attorney with the appropriate undergraduate field, and also the conflict of interest for those in that field also working for the "big pharma" as small entity inventors in that field could not support said qualified attorneys.)

Applicant's amendment submitted July 22, 2009, necessitates the following new grounds of rejection: **Claim Rejections** - 35 USC § 112 The following is a quotation of the first paragraph of 35 U.S.C. 112: The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention. Claims 140, 141, 143, and 144 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)	This had been discussed above prior to the line-by-line reply. (Herein we revisit some of the issues with more specifics).

contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's amendment submitted March 13, 2009 with respect to the aforementioned claims has been fully considered and but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for a method comprising discussing **all of the** specific considerations recited in the claims **with a patient**. *Although the specification and the priority document 60/319436 do disclose these factors as considerations for physicians to take into account in the treatment of depression*, they do not teach or disclose discussing them with a patient. As the instant specification as filed contains no description of this method the specification as originally filed does not provide support for the subject matter of instant claims 140, 141, and 143. See in re Smith, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972). Because Applicant's amendment necessitated this new ground of rejection, the rejection is made FINAL.The following rejections of record in the previous office action are maintained: Claim Rejections - 35 USC § 112 The following is a quotation of the first paragraph of 35 U.S.C. 112: The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.	The applicant traverses these statements: **It was clearly described** in both the specification and the provisional application, **that the health care provider needs to discuss the risk/benefit/alternatives with the patient(s)** and involve them in the decision making. We were very careful of pasting to the claims the "items/specific considerations" in using the exact phrases used in the specification). **All of these "items or specific considerations" are falling within the risk/benefit alternative discussion, and as such it was disclosed that these need to be discussed with the patients**. If absolutely needed, some of the words discussed can be substituted with disclosed (as we definitely disclosed these considerations in our specifications). The word "steps" were only used in the claims to emphasize to the examiners the patentability (that If it is felt (for some unknown reason to the applicant) that the word step is the one that the examiners objected to, then that word can be replaced with alternate phrase (like "discussion of the following risk/benefits". If that is the case, I do not see why the PTO would not see any claims allowable, and why the PTO would not assist with claim drafting assistance. At minimum the applicant needs specifics of what exactly

	(what words or phrases) the PTO was objecting to.
Claims 1-9, 11-12, 37, 38, 41-43, 48-50, 53-71, 96-103, 126, 131-145, and 147 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating depression, cognitive distortions, smoking cessation, or nicotine withdrawal comprising administering certain antidepressants defined in the specification and prior art, does not reasonably provide enablement for such a method involving any antidepressant whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.	We have also addressed these objections in our prior replies. The applicant is puzzled of how come the PTO cannot help with claim drafting assistance, when the objection/issue of "any" antidepressant – in a worst case scenario - **could be resolved by listing currently approved antidepressants that we have also listed for example under claim 10 or 14, and many recited in claims15-35**. That should have overcome of the "any antidepressant" objection. If the underlying claim that others are dependent from is objected these claims can be merged with that language. So how come the PTO does not able to help the applicant? (Re: MPEP, Section 707.07 (j))
The Applicant's attention is drawn to In re Wands, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. Nature of the invention: The claimed invention is a method of treating depression and other disorders by administering a drug or a combination of two drugs. It is claimed that the antipsychotic drug improves the therapeutic outcome even in patients not suffering from psychotic symptoms. The state of the prior art: Combination therapy with antidepressants and atypical antipsychotic drugs has been taught in the prior art. Although a number of drug combinations have been tested and found to be useful, particularly combinations of a serotonin reuptake inhibitor with an atypical antipsychotic, many drugs of both types have not been tested. In particular, typical antipsychotics and dopamine system stabilizers such as aripiprazole have not been tested in the claimed methods. More generally, the full limits of the class of compounds known under the various functional groupings (e.g. selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, antidepressants with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, antidepressants with serotonin/norepinephrine/dopamine reuptake inhibition, etc.) recited in the language of instant claim 1 have not been determined, and it is likely that there exist novel compounds with antidepressant activity that have not yet been discovered. The relative skill of those in the art: The relative skill of those in the art is high. The predictability or unpredictability of the art: *The interaction between two classes of drugs is dependent on the specific mode of*	As regards to the currently known antidepressants this would not be an objection, as the PTO said earlier for the medications that can be used off label.

action of the two drugs. In the absence of any general theory explaining the action of atypical antipsychotic drugs to enhance therapeutic outcomes with antidepressants, it is not possible to predict the efficacy of any particular antipsychotic for this purpose absent experimental data. Because so many different compounds are known as antidepressants no one example of group of related examples can be predictive for demonstrating the effectiveness of antidepressants combined with antipsychotics generally. Thus the effectiveness of a particular combination therapy of an antidepressant and an antipsychotic for the treatment of depression, cognitive distortions, smoking cessation, or nicotine withdrawal is unpredictable. The Breadth of the claims: The claimed invention encompasses combination therapies of any of a number of functionally defined groups of antidepressants with an antipsychotic, particularly a typical antipsychotic, an atypical antipsychotic, or a dopamine system stabilizer. The antidepressants are defined only by their functional characteristics. In particular, a vast number of different structures are included within the limits of these claims. The amount of direction or guidance presented: Two hypothetical cases are given in order to illustrate possible uses of the claimed therapeutic method. (p. 16-17) The presence or absence of working examples: No working examples of the claimed therapeutic methods are provided by Applicant. Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as antidepressant/antipsychotic combination therapy. See MPEP 2164. The quantity of experimentation necessary: In order to practice the claimed invention, one skilled in the art would be required to determine the extent of antidepressants useful in said methods. Because Applicant has provided no working examples, and because the state of the art is unpredictable, many different antidepressants would need to be tested in order to provide a comprehensive understanding of which combinations are or are not useful in the claimed method. Because there is no structural limitation to the full scope of the various functionally defined groups of antidepressants, one skilled in the art would have to discover each and every possible compound with antidepressant activity. Doing so would require the synthesis and testing of an enormous number of compounds. In the process of synthesizing the compounds to be tested, many novel and unpredictable synthetic methods would have to be developed. These experiments would be repeated many times in animal models of depression, cognitive distortions, and nicotine addiction, in order to establish their suitability as therapeutic methods. It should be noted that	This again is an incorrect statement and reflects that the examiners did not read (or are unfamiliar with) our specification and replies. This is a highly incorrect statement by the PTO. The specification provides far more guidance then the examples. **The guidance in the specification is very extensive and attends to many different details that the skilled in the art might have experienced obstacles without said specific guidance.** The combination of antidepressants/antipsychotic is not an unpredictable and not an undeveloped art. The number of prior art patent publications that were presented by the PTO also attests to that fact. (Yet these prior art documents could not provide a solution to the problems unsolvable by others and to the claims presented in this invention.).

evaluating psychological disorders such as depression and cognitive distortions in animals is more difficult than evaluating a therapy for a nonpsychological condition such as cancer or arthritis. Because of the unpredictability of the art and the lack of any generalized method for predicting the pharmacological properties of any arbitrarily chosen molecule, these animal experiments would need to be repeated many times, and involve the maintenance, killing, and disposal of many experimental animals, to establish the suitability or lack thereof for each compound found to possess the desired activity in vitro. The scale of synthesis, in vitro, and in vivo testing described in the preceding paragraphs would present an undue amount of unpredictable experimentation to require of anyone wishing to practice the invention. Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." Therefore, in view of the Wands factors, as discussed above, particularly the unpredictability of the art and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention with all of the compounds falling within the recited functional groupings of antidepressants.	
Response to Argument: Applicant's arguments, submitted July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that other issued US patents use the non-enabled terms and that therefore these terms should be given enablement for this application. However, <u>each patent is treated on its own merits</u>, *and the fact that a particular term appears in an issued patent is not a valid argument in favor of its enablement in a completely different patent.*	Since there is such a wide gap between the understanding of the applicant and the PTO, an explanation would be still expected from the PTO of how come the same terms (like SSRI's, etc) that the PTO objects in this instant claim were allowed to be used in the other patents. Please note that the applicant has not asked to be granted a patent just because the PTO erred in other instances, but the discussion and explanation by the PTO on how come in these other instances a wide description of "functional" description of medication categories (where new medications in that class could be discovered just as much as in the instant case) would help the applicant. PTO regulations (MPEP, Section 707.07 (j)) specifically require patent examiners to help inventors in pro se (no lawyer) cases.

Applicant also argues that the claims 140-143 are clearly enabled in a different way in the specification. These claims all depend from claim 1, and do not further limit the species of the antidepressant being used. They merely introduce additional steps involving consultation with the patient, which do not help one skilled in the art to obtain the needed combination of an antidepressant and an antipsychotic. Therefore they raise the same issues of enablement as the base claim.	As said before (in this box above): The "any" antidepressant objection – in a worst case scenario - **could be resolved by listing currently approved antidepressants that we have also listed for example under claim 10 or 14, and many recited in claims15-35**. That should have overcome of the "any antidepressant" objection. If the underlying claim that others are dependent from is objected these claims can be merged with that language. In a worst case scenario, the claims 140 could be amended and merged with claim 1 or 2, using the specific list of antidepressants (and atypical antipsychotics) from claim 10 or 14 and 15-35. So how come the PTO does not able to help the applicant? (Re: MPEP, Section 707.07 (j))
Applicant further argues that the instant disclosure provides the successful conclusion of *search* that is necessary to warrant patent protection. However, Applicant's disclosure is not a disclosure of novel research on antidepressant and antipsychotic pharmacotherapy. Rather, by Applicant's own admission, it as a synthesis of prior art elements. Therefore the facts disclosed by Applicant do not go beyond what is already known in the prior art. The only addition is a suggestion to combine prior art elements in a new manner. For Applicant's invention to be sufficiently complete and predictable for one skilled in the art to practice it, it must be predictable which antipsychotics can be combined with which antidepressants to achieve an augmenting effect. While Applicant's own teaching provides a suggestion for using various combinations of active agents, the enablement for such a combination will depend on what is known in the prior art about the utility of these drugs and their synergistic or antagonistic interactions. <u>For combinations that have already been explored in the prior art, for example an atypical antipsychotic and a selective serotonin reuptake inhibitor, the combination can be enabled without further disclosure from Applicant</u>. For other combinations, for example a combination of a typical antipsychotic and an NMDA receptor antagonist, the prior art does not	Search?? That must be the PTO's word. (Please refer to the discussion before the line-by-line reply). That objection – by the PTO's own admission is not applicable for the currently used antidepressant and antipsychotics. <u>If we do not include currently non-approved medications this would no longer an issue (the "NMDA")</u>. However, this is an incorrect statement, as the various [and

give any reason to believe that the same augmenting effect would be present. Note that, while Applicant has provided a theoretical basis for synergism based on treatment of cognitive distortions, increased compliance, more rapid onset of action, and so forth, *there is no concrete evidence that this mechanism is what is responsible for the observed augmentation effect of typical antipsychotics on selective serotonin reuptake inhibitors*. If, for example, the augmenting effect is based on the actions of both of these drug classes on the serotonin neurotransmitter system, then the combination therapy would not work for antidepressants that do not affect serotonin, for example substance P antagonists or NMDA receptor antagonists. Applicant further argues that actual working examples are not required for patentability and are prohibitively expensive for a small entity to undertake. Applicant gives the example of a small entity seeking patent protection for a spacecraft design. However, any idea that is sufficiently **novel** to warrant patent protection will require some sort of proof. The standard for enablement is not what the particular applicant can be expected to accomplish with his own limited resources but rather **what scope of invention the public can be reasonably sure of having possession of** in exchange for patent protection. In the case of a spacecraft, there would have to be a reasonable expectation that the spacecraft would actually function as described. Simply providing a spacecraft design whose functionality is unknown, (for example one that includes a novel type of engine that has never been successfully used) and asserting that the inventor does not have the resources to test it would not enable the spacecraft design. In the instant case, Applicant is claiming methods involving a wide variety of different antidepressants, many of which are not	combined] effects of how an antipsychotic may act in the desired direction for depression, cognitive distortion, or prevention of suicide, had been all disclosed (with the collection of a vast amount of prior art references). In addition in how the antipsychotic medications would achieve their specific and required effect the recognition of the extensive depressive symptoms (in addition of what is used in the diagnostic criteria [DSM®]), and the recognition of what we (later named pseudo-placebo effect) also play a role. [The later named pseudo-placebo effect was described in details the (provisional) application]. In our reply to the 4th OA (March 11, 2009) we brought attention to two studies in support of our invention: "Most recently a double bind placebo controlled study sponsored by a drug company had shown that unexpected effect. In that study about 6 and a half years later then our priority date the patients in that study had suicidal ideation but the group of patients had treatment resistant depression. **(Reeves H et al Efficacy of risperidone augmentation to antidepressants in the management of suicidality in major depressive disorder: a randomized, double-blind, placebo-controlled study. J. Clin Psychiatry 69:8 August 2008)** An earlier case study that is not a prior art also showed that all patients in the publication receiving combination treatment stopped having suicidality, and showed improvement. All those patients had resistant depression. **(Viner MW et al Low-dose risperidone augmentation of**

used in the prior art. Applicant's invention further depends on the augmentation of antidepressants by antipsychotic drugs without any clear teaching as to what factors are required for this augmentation to occur or whether it will really be present for **any** combination of an antidepressant and an antipsychotic regardless of the mechanism by which the two drugs work. Simply stating that two broad classes of drugs can by used together does not enable one skilled in the art to use them together if the results would be unpredictable. Applicant further argues that the state of the art has shifted towards enabling patentability in the time since the filing of the invention. While Applicant has provided examples (for example **Reeves** et al. included with PTO-1449) these examples are directed toward combinations of specific classes of drugs (for example a typical antipsychotic and a selective serotonin reuptake inhibitor) and are not seen in the prior art as applicable to all antidepressants or all antipsychotics. For these reasons the rejection is deemed proper and made FINAL.	**antidepressants in nonpsychotic depressive disorders with suicidal ideation. Journal of Clinical Psychopharmacology 23:1 2003).”** In addition the marketing of aripriprazole (e.g. in TV advertisement) would likely infringe on this invention (if issued) as no time frame is mentioned in that ads of when augmentation with this drug should occur “if the antidepressant is not working”. The FDA only approved it for the treatment of treatment resistant depression, but the advertisement does not specify that. Although these (underlying) experiments were not done by the applicant is can give an assurance to the public for “what scope of invention the public can be reasonably sure of having possession of in exchange for patent protection.” All of these references are not prior art documents and the PTO errs on bringing up Reeves as prior art. (see also discussion before the line-by-line reply).

Claim 65 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant's amendment submitted January 8, 2007 with respect to claim 65 has been fully considered and but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for the active metabolite of risperidone. As the instant specification as filed contains no description of said metabolite or a method of using it as a therapeutic agent, the specification as originally filed does not provide support for the subject matter of instant claim 65. See in re Smith, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972). Response to Argument: Applicant's arguments, submitted July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the cited articles concerning grape juice are not relevant because they do not fit the facts of Applicant's analogy. Even disregarding whether grapes and grape juice are identical, Applicant's analogy does not accurately represent the facts of the present case.	Claim 65 is now cancelled.

The analogy presented is that if grapes and grape juice were shown to have the same effect, then using grape juice would be inherent in using grapes. However, when this condition is attached to Applicant's arguments, this is not seen to be analogous for the situation of risperidone and its active metabolite. Administering an active metabolite is not necessarily the same as administering the precursor of said metabolite. The active metabolite could differ in its bioavailability, stability, shelf life, or rate of excretion, for example. Therefore the actual physiological effect of administering a given dose of the active metabolite of risperidone by a given route is not expected to be the same as the effect of administering the same dose of risperidone by the same route. The physical dosage form administered in each case would be a different composition of matter. Therefore the two methods are not identical and a disclosure describing one does not necessarily describe the other absent a specific description of both the parent drug and the active metabolite. Thus the rejection is deemed proper and made FINAL	

Claim Rejections - 35 USC § 103 The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action: (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made. Claims 1-6, 11, 13, 37, 38, 41-43, 48, 49, 53, 54, 56, 58, 59, 119-121, 123, 126129, 142, 145, and 146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Howard. (US patent publication 2002/0123490, of record in previous action) Howard discloses a combination of a serotonin reuptake inhibitor and an atypical antipsychotic, as well as a method for using this combination to treat obsessive compulsive disorder, psychosis, and depression. (p. 1, paragraph 0004) Depressive disorders treated include major depressive disorder, as well as atypical depression including anxiety. (p. 1, paragraph 0008) Anxiety is reasonably considered to be as cognitive distortion as it involves disordered cognitions such as overestimation of risk. Although treatment of refractory depression is a preferred embodiment, all depression including depression not found to be refractory, is included within the range of disorders to be treated. The amounts of each agent used are such that the combined effect has improved efficacy compared to either component individually. (p. 1 paragraph 0005) Atypical antipsychotics used in the invention include abaperidone, belaperidone, clozapine, iloperidone, olanzapine, perospirone, risperidone, sertindole, tiospirone, ziprasidone, zotepine, quetiapine, and blonanserin. (p. 7 paragraphs 0172-0198) The two agents are to be administered in dosages of about 5-200 mg/day of the antipsychotic agent and about 2.5-500 mg/day of the serotonin reuptake inhibitor. (p. 8 paragraph 0233) The compounds can be administered by various dosage forms including oral administration. (p. 9 paragraphs 0235-0236) Howard does not specifically disclose a method wherein the therapeutic agents are administered as soon as possible. It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Howard as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Howard already discloses the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer	This had been discussed above prior to the line-by-line reply (and also in prior replies to the OAs).

a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art. Note that "as soon as possible" is an extremely broad limitation that would include practically any method wherein treatment was not deliberately delayed. Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art. Thus the invention taken as a whole is prima facie obvious.

Response to Argument: Applicant's arguments, submitted July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the reference would not be enabled for the purpose of the claims, specifically because Howard et al. discloses treating refactory depression as a preferred embodiment of the disclosure. However, the range of conditions to be treated is described as "depression, especially refactory depression." One of ordinary skill in the art would have understood this limitation as indicating utility for treating depression generally, and only including refactory depression as an especially preferred embodiment. Preferred embodiments do not remove enablement for nonpreferred embodiments. One of ordinary skill in the art would have thus understood Howard et al. as teaching two embodiments, treatment of refactory depression and treatment of nonrefactory depression. It would have been obvious to use the invention for either one of these categories individually.

Applicant further argues that it would not be obvious to administer the therapy of Howard et al. "as an initial treatment, as soon as possible, or upon presentation of said patient to a physician," because it would not in fact be indicated at said time due to clinical guidelines. Applicant further argues that the time frame for administration is further limited by the requirement that the depression be non-treatment-resistant. According to the definition in paragraph 0916 of the provisional application 60/319436, treatment resistant depression is defined as depression wherein the patient has had two unsuccessful courses of antidepressant therapy for six weeks each. Nothing in the disclosure of Howard or the other prior art would have made one of ordinary skill in the art determine that this therapy could not have been used as an initial therapy or a second therapy.

Applicant further argues that the present application reveals a new risk benefit analysis that is different from what is used in the art. Firstly, claims 140, 141, 143, and 144 as amended are now clearly directed toward a therapeutic method involving steps wherein the physisican discusses certain specific topics with the patient. Therefore these claims are no longer rejected as obvious over Howard et al., because one of ordinary skill in the art would not have had any reason from the reference to discuss those specific topics. For the other claims, the claims are broad enough to encompass obvious embodiments. For example, "as soon as possible," is interpreted to mean as soon as one of ordinary skill in the art would have considered the therapy to be a reasonable course of action. If, as alleged by Applicant, malpractice considerations would have kept one of ordinary skill in the art from using the therapy at a certain time, it is not "possible" to use it at that time, under the broadest reasonable interpretation of the claims. See the notes on claim interpretation below.

As regards the supposed new information disclosed by Applicant, the examiner, contrary to Applicant's allegation, has read the entire specification, as well as the provisional application 60/319436. The only new information provided consists of a recap of prior art knowledge about the treatment of depression and other psychiatric disorders, speculation as to how antipsychotics could improve certain contributing aspects of depression such as

cognitive distortions which otherwise complicate its treatment with antidepressants alone, statements of opinion regarding the trade-off between the side effects of antipsychotic medication and its expected benefit in improving depression, and two hypothetical examples of how the invention would be expected to work if Applicant's speculations are correct. None of these aspects are considered to be new information, as opposed to new opinions. Opinions are not patentable. For these reasons the rejection is deemed proper and made FINAL.	

Claims 1, 2, 4, 6, 10-15, 18, 22, 26, 30, 36-38, 41, 42, 48, 51-53, 56, 58-60, 109118, 124, 125, and 140-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tollefson et al. '921 (US patent 5958921, of record in previous action, different from Tollefson W099/61027 cited previously) in view of the Merck manual of diagnosis and Therapy. (Merck, of record in previous office action) Tollefson '921 discloses a method of treating major depression comprising administering an effective amount of olanzapine. (column 1 lines 30-55) A dose of 2.530 mg per day is recommended. (column 2 lines 23-25) Olanzapine can be formulated as tablets for oral administration. (column 4 lines 5-25) Tollefson '921 does not disclose a method further comprising administering an antidepressant, for example one of the various serotonin reuptake inhibitors recited in the claims. Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine. It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with olanzapine as disclosed by Tollefson '921. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art. It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Tollefson '921 as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Tollefson '921 and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art. Finally, it would have been obvious to one of ordinary skill in the art to administer olanzapine in a low dose. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves. Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art. Thus the invention taken as a whole is prima facie obvious. Response to Argument: Applicant's arguments, submitted July 22, 2009, have	This had been discussed above prior to the line-by-line reply (and also in prior replies to the OAs).

been fully considered and not found to be persuasive to remove the rejection. Applicant argues that Tollefson et al. '921 is not enabled because the depressive patients not diagnosed as psychotic who are referred to in the patent and in the associated clinical trial might possible be actually suffering from unrecognized psychosis. Applicant also speculates that no ethics committee would have approved the double-blind study referenced by Tollefson. All of these arguments are speculation by Applicant and to not provide any concrete evidence of non-enablement. An issued US patent is presumed to contain an enabling disclosure for, at the vary least, the subject matter of the issued claims. Proving non-enablement of an issued patent requires concrete evidence, not speculation that it is improbable that the invention.actually works. Therefore the rejection is deemed proper and made FINAL.	

Claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, 109-122, 124, 126-130, and 140-143 are rejected under 35 U.S.C. 103(a) as being obvious over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 Al, of record in previous office action) Chappell et al. discloses a method of treating depression, anxiety, or psychosis in a mammal by administering a combination of an antidepressant, a D4 receptor antagonist, (an antipsychotic) and a pharmaceutically acceptable carrier. (p. 1, left column, paragraph 0002) Note that anxiety is reasonably considered to be a cognitive distortion as it involves unreasonable patterns of thought, namely excessive or irrational worry and exaggeration of problems or threats. Phobias and panic disorders are also considered to be cognitive distortions. General types of antidepressants which can be used are listed in paragraph 0021 and include norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, and monoamine oxidase inhibitors, among others, as described in instant claims 11-13. Selective serotonin reuptake inhibitors include fluoxetine, fluvoxamine, paroxetine, and sertaline. (p. 3, paragraph 0025) Norepinephrine reuptake inhibitors which may be used are listed in paragraph 0023 and include clomipramine among others, as in instant claims 14 and 15. Other useful antidepressants are listed in paragraph 0181 on p. 8. The compounds used in this invention may all be administered orally, as described by instant claim 38. (p. 22, paragraphs 0460-0462) Various dopamine D4 receptor antagonists can be used, as listed on pp. 15-21. In particular, p. 20, paragraph 0446 lists olanzapine as a useful D4 receptor antagonist. D4 receptor antagonists can be administered in a preferred dose of about 5 to about 500 mg per day. (p. 22, paragraph 0459) Chappell et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider. Chappell et al. does not disclose a method where in the antipsychotic is administered in a dose of 2.5-10 mg olanzapine. It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Chappell et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Chappell et al. already discloses the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art. It would also have been obvious to one of ordinary skill in the art at	This had been discussed above prior to the line-by-line reply (and also in prior replies to the OAs).

the time of the invention to practice the method of Chappell et al. using a dose of 5-10 mg of olanzapine per day. One of ordinary skill in the art would have been motivated to use this rang, and would have reasonably expected success in doing so, because the range disclosed by Chappell et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen. When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1]. Further, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art. Thus the invention taken as a whole is prima facie obvious. Response to Argument: Applicant's arguments, submitted July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that D4 antagonists are not necessarily antipsychotics. As discussed in the previous office action, Chappell et al. does not merely teach D4 receptor antagonists as a generic class. The reference also specifically exemplifies olanzapine, a known antipsychotic, which is explicitly stated in several claims such as claims 10, 18, 22, or 26 as being an embodiment of the claimed invention. The test for obviousness is not whether the reference discloses the same motivation as the prior art for practicing the claimed invention but whether it discloses any motivation for practicing any embodiment of the claimed invention. According to MPEP 2144, the reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. >See, e.g., In re Kahn, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings.");< In re Linter, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991) Therefore it is not necessary that the prior art reference specifically disclose that the reason olanzapine works in this combination is because of its antipsychotic activity and not merely because of its D4 receptor antagonism. Furthermore Applicant argues that Chappell discloses treatment of depression broadly without specifically excluding treatment resistant or psychotic depression. However, a broad teaching of utility for depression would be understood by one of ordinary skill in the art as including both treatment resistant and non-treatment-resistant depression, as well as both psychotic and non-psychotic depression. Again, Applicant has given no reason to believe that the prior art's statement of depression in general is really meant to apply only to treatment resistant or psychotic depression. Applicant additionally argues that the office action does not disclose whether the activity of olanzapine is due to its D4 activity. The test for whether the prior art teaches a particular element of the invention is whether or not it teaches that particular element, in this case a combination of olanzapine with an antidepressant. Whether or not the D4 antagonist activity is responsible for treatment of depression is not relevant.	

Applicant further argues that anxiety and cognitive distortions are separate conditions and that anxiety is not a cognitive distortion. Applicant's argument for this position is, according to the previous response filed May 1, 2008, that anxiety is not always pathological, and that anxiety due, for example, to a totalitarian society or an abusive boss is rational and does not involve cognitive distortions. However, Chappell et al. specifically (on p. 1 paragraph 0010) defines anxiety as including anxiety disorders. Anxiety disorders are a pathological condition distinct from the reasonable feelings of anxiety experienced in adverse situations like those described. Applicant further argues that anxiety and cognitive distortions are not the same. However, all that is required for obviousness is that cognitive distortions are one element present in anxiety disorders. Even though anxiety disorders incorporate other elements besides cognitive distortions, the cognitive distortions are there and are an element of the disorder being treated. For these reasons the rejection is deemed proper and made FINAL.	

Claims 106-108, 131-134, and 136-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 Al, of record in previous office action) in view of Berman et al. (Reference of record in previous action) The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method in which the antidepressant is ketamine. Berman et al. discloses that ketamine, which acts on the NMDA receptor, exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph) It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as the antidepressant in the method of Chappell et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the antidepressants recited by Chappell et al. One of ordinary skill in the art would reasonably have expected success because Ketamine is already known to be useful as an antidepressant. Thus the invention taken as a whole is prima facie obvious. Response to Argument: Applicant has not provided any arguments specifically treating the combination of Chappell et al. with Berman et al. Applicant's arguments with respect to Chappell et al. alone are discussed above. Therefore the rejection is maintained and made FINAL.	This had been discussed above prior to the line-by-line reply (and also in prior replies to the OAs).

Claims 5, 16, 17, 20, 21, 24, 25, 28, 29, 32-35, 64, 75, 76, 79, 80, 83, 84, 87, 88, 91-94, 123, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 Al, of record in previous office action) as applied to claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, and 109-122, 124, and 126-30 above, and further in view of Schmidt et al. (Reference of record in previous action) The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using ziprasidone, risperidone, or quetiapine as the antipsychotic agent. Schmidt et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 198, table 1) In particular, ziprasidone, risperidone, olanzapine, and quetiapine are all shown to have affinity for the D4 receptor. It would have been obvious to one of ordinary skill in the art at the time of the	This had been discussed above prior to the line-by-line reply (and also in prior replies to the OAs).

invention to use ziprasidone, risperidone, or quetiapine as the dopamine D4 antagonist in the invention of Chappell et al. One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as therapeutic agents in this invention. Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art. Thus the invention taken as a whole is prima facie obvious. Response to Argument: Applicant's arguments, submitted July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant again argues that the reference does not disclose a link between antipsychotic activity and D4 receptor antagonism for the claimed compounds. This argument is dealt with in the rejection of Chappell et al. alone and is not found to be persuasive. Therefore the rejection is deemed proper and made FINAL.	

Claims 5, 9, 16, 20, 24, 28, 64, 75, 79, 83, 87, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 Al, of record in previous office action) as applied to claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, and 109-122, 124, and 126-30 above, and further in view of Roth et al. (Reference of record in previous action) The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using risperidone, trifluoroperazine, or zotepine as the antipsychotic agent. Roth et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 366, table 1) In particular, risperidone, olanzapine, trifluoroperazine and zotepine are all shown to have affinity for the D4 receptor. It would have been obvious to one of ordinary skill in the art at the time of the invention to use risperidone, trifluoroperazine, or zotepine as the dopamine D4 antagonist in the invention of Chappell et al. One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as therapeutic agents in this invention. Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art. Thus the invention taken as a whole is prima facie obvious. Response to Argument: Applicant has not provided any arguments specifically treating the combination of Chappell et al. with Roth et al. Applicant's arguments with respect to Chappell et al. alone are discussed above. Therefore the rejection is maintained and made FINAL.	This had been discussed above prior to the line-by-line reply (and also in prior replies to the OAs).

Claims 1-3, 9, 11-15, 37, 38, 41-43, 48, 49, 53-62, 69-74, 96-105, 129, 142, and 145 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. (Reference of record in previous action) as applied to claims 126-128 above, and further in view of the Merck Manual of Diagnosis and Therapy, Seventeenth Edition. (Reference of record in previous action, herein referred to as Merck) Robertson et al. discloses a number of studies of the antidepressant activities of major tranquilizers (also known as typical antipsychotics). (p. 173, last paragraph) In particular, perphenazine and combinations of perphenazine with	This had been discussed above prior to the line-by-line reply (and also in prior replies to the OAs).

amitriptyline were used in treating patients suffering from depression, including non-psychotic depression. (p. 179, paragraphs 4-5) Perphenazine was found in one study to be particularly effective, while a combination of perphenazine and amitriptyline was found to be effective for treating other types of depression. It is noted that anxiety is reasonably considered to be a cognitive distortion as it involves unreasonable patterns of thought, namely excessive or irrational worry and exaggeration of problems or threats. Flupenthixol, (p. 183, paragraphs 4-6) and sulpride, (p. 185, paragraphs 1-2) are also seen to possess antidepressant activity. The intended uses recited in the instant claims, for example inhibiting the development of tolerance toward an antidepressant, providing a neuroprotective effect, avoiding worsening of the depression, resisting suicide, avoiding suicidal ideation, and delaying or resisting relapse, are inherently present in any circumstance where the claimed drugs are administered to a patient suffering form depression, as all depressed patients are at elevated risk for suicide, and could suffer relapse after treatment. Robertson et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering a low dose of the antipsychotic. Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine. It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with the typical antipsychotics of Robertson et al. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art. It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Robertson et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Robertson et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art. Finally, it would have been obvious to one of ordinary skill in the art to administer the antipsychotic in a low dose. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of typical antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves. Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art. Thus the invention taken as a whole is prima facie obvious. Response to Argument: Applicant's arguments, submitted July 22, 2009, with respect to the above grounds of rejection, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the art developed a consensus against using antipsychotic drugs for treating depression. The evidence cited by Applicant appears to be the citation of a couple paragraphs in	

the specification that furthermore cite short passages from several prior art reviews. None of the cited documents (Nelson, Price, or Zimmerman) appear to have been included among the information disclosure statements submitted by Applicant. Based on Applicant's citation, it appears that the argument is that the art never recommended antipsychotic augmentation in non-psychotic depression because "the risk/benefit ratio ... generally does not favor [antipsychotic augmentation]." This reflects a decision in the art, not that the previous evidence of antidepressant activity was absent or non-enabling, but that newer approaches worked better. The mere fact that a new approach is better does not thereby render an older, less effective approach non-enabled or non-obvious. It is still obvious, but it is simply not used. Therefore the rejection is deemed proper and made FINAL.	

Claims 106-107 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. (Reference of record in previous action) in view of Berman et al. (Reference of record in previous action) The disclosure of Robertson et al. is discussed above. Robertson et al. does not disclose a method in which the antidepressant is ketamine. Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph) It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as an antidepressant in combination with a typical antipsychotic recited in the method of Robertson et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the therapies recited by Robertson et al., namely treating depression. One of ordinary skill in the art would reasonably have expected success because Ketamine is already known to be useful as an antidepressant. Thus the invention taken as a whole is prima facie obvious. Response to Argument: Applicant's arguments, filed July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection, for reasons recited as regards the rejection over Robertson et al. in view of Merck above, and are not found to be persuasive for the same reasons. Therefore the rejection is deemed proper and made FINAL.	This had been discussed above prior to the line-by-line reply (and also in prior replies to the OAs).

Claims 1, 2, 4, 5, 6, 10-14, 16-18, 20-22, 24-26, 28-30, 32-38, 41-43, 48, 49, 5164, 66, 70-77, 79-81, 83-85, 87-89, 91-105, 109-122, 124-129, and 145-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pivac et al. (Reference included with previous action) in view of Merck (Reference of record in previous action) Pivac et al. discloses that atypical antipsychotics such as risperidone or olanzapine, should be coadministered with selective serotonin reuptake inhibitors, because they produce a synergistic effect. (p. 236, left column, last paragraph, right column first paragraph) Pivac et al. does not disclose a therapeutic method using the specific SSRIs fluoxetine, paroxetine, sertaline, or fluvoxamine, or the atypical antipsychotics ziprasidone or quetiapine. Pivac et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering a low dose of the antipsychotic. Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various	This had been discussed above prior to the line-by-line reply (and also in prior replies to the OAs).

antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine. Merck et al. also discloses a listing of atypical antipsychotics, including clozapine, risperidone, olanzapine, quetiapine, sertindole, and ziprasidone. (p. 1570, table 193-4)
It would have been obvious to one of ordinary skill in the art at the time of the invention to use the various SSRIs and atypical antipsychotics disclosed by Merck in the method of Pivac et al. One of ordinary skill in the art would have recognized that the specific compounds disclosed by Merck fall within the broad classes described by Pivac et al., and can thus be used in the disclosed method. Substituting these known prior art compounds in a known prior art method is well within the ordinary and routine level of skill in the art.
It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Pivac et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Pivac et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.
Finally, it would have been obvious to one of ordinary skill in the art to administer the antipsychotic in a low dose. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of typical antipsychotic drugs. One of ordinary skill in the art would have reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves.
Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.
Thus the invention taken as a whole is prima facie obvious.
Response to Argument: Applicant's arguments, filed July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant
reiterates the unconvincing line of argument regarding Ferris et al. from the previous communication. As discussed in the previous office action, Ferris et al. does not contain any teaching as to combination of antipsychotics with SSRI antidepressants, because SSRI antidepressants were not in common use at the time of publication. In any case, Applicant's statements regarding receptor profile are not relevant, because a finding of obviousness does not depend on the prior art process working by a particular receptor. Regardless of what mechanism the augmentation takes place by, it still falls within the limits of the claimed invention. Applicant's further arguments appear to rest on the assertion that his method has never been used before. However, this is flatly not the case, as Pivac et al. specifically discloses combining SSRIs and atypical antipsychotics for the treatment of depression. The only differences between this disclosure and Applicant's claims regard the use of specific SSRIs, and the timing and dosage of administration, which are routine in the art.
The papers cited by Applicant to substantiate his position do not actually suggest that Pivac et al. is not enabled. For example, Cremers et al. does not dispute the fact that 5-HT1A antagonists can augment SSRI antidepressants. (p. 13 right column last paragraph) The reference merely questions a particular theory as to how this effect happens. Roth et al. merely discloses that the effect of mianserin on 5-HT2 receptor binding is not due to an alteration in mRNA levels. Toth et al. comes to an opposite conclusion. Neither of these references

suggests that atypical antipsychotics would not have an augmenting effect on SSRI antidepressants as described by Pivac et al. Regarding Perez et al., the reference is not relevant to the instant case because it merely teaches that adding pindolol to a previously ineffective SSRI in treatment resistant patients does not reverse the treatment resistance. This teaching only concerns treatment resistant patients, and while it could be evidence against enablement of a method of treating treatment resistant depression, it does not give any clear teaching that could be applied to non-treatment-resistant depression. The rest of Applicant's argument appears to be a bald assertion that Applicant's method is somehow different from the prior art, without any clear evidence. Therefore the rejection is maintained and made FINAL. Claims 1-4, 7, 8, 10-15, 19, 23, 27, 31, 36-38, 41-43, 48, 49, 51-63, 67, 68, 70-74, 78, 82, 86, 90, 95-105, 109-122, 124-130, and 145-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan et al. (PCT international publication W002/060423, reference of record in previous action) in view of Merck. (Reference of record in previous action) Jordan et al. discloses a method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT1A receptor, comprising administering a compound having a given structure. (p. 15, lines 5-18) According to the Chemical Abstracts Registry entry 129722-12-9, (reference of record in previous action) this structure is aripiprazole. This compound is useful for treating various disorders of the central nervous system, for example major depression and melancholia, as well as various cognitive distortions including obsessive compulsive disorder, alcohol and drug addiction, and cognitive impairment. (p. 16, line 23 — p. 17, line 10) The preferred unit dosage form is 1-20 mg of active agent. (p. 18, lines 5-10) Jordan et al. does not disclose a method comprising administering aripiprazole in combination with an antidepressant. Jordan et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering 2.5-15 mg of aripiprazole. Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine. It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with the typical antipsychotics of Jordan et al. to a patient suffering from major depression either alone or complicated by any of the various cognitive distortions recited by Jordan et al. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art. It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Jordan et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Jordan et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from	

among the various options available in the prior art is within the routine and ordinary level of skill in the art. It would also have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Jordan et al. using a dose of 2.5-15 mg of aripiprazole per day. One of ordinary skill in the art would have been motivated to use this rang, and would have reasonably expected success in doing so, because the range disclosed by Jordan et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen. When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); In re Woodruff, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1]. Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art. Thus the invention taken as a whole is prima facie obvious. Response to Argument: Applicant's arguments, filed July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that one of ordinary skill in the art would not have been enabled for using aripiprazole in the claimed invention, because it was not approved and because it had not been used for treating cognitive distortions or treatment resistant depression, and further because the analogous compound buspirone is not used, either with FDA approval or off-label, to treat depression. The fact that those in the art do not use a particular therapy is not persuasive for a finding of non-enablement, as discussed below in the section "Further considerations". Regarding the reference Landen et al., as is the case earlier with Perez et al., the reference concerns treatment-resistant depression. The fact that a therapy does not work against treatment resistant depression does not prove it will not work against non-treatment resistant depression, as the very definition of treatment resistant depression specifies that it is more difficult to treat then ordinary depression, and not all therapies that are effective against non-treatment resistant depression will work against treatment resistant depression. What would be needed for evidence of non-enablement would be evidence that the combination does not work, or have any benefit over monotherapy, for the non-treatment-resistant depression that is treated in the instant claims. Therefore the rejection is deemed proper and made FINAL.	

Claims 106-108, 131-133, and 135-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan et al. (Reference of record in previous action) in view of Berman et al. (Reference of record in previous action) The disclosure of Jordan et al. is discussed above. Jordan et al. does not disclose a method in which the antidepressant is ketamine. Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph) It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as an antidepressant in combination with a typical antipsychotic recited in the method of Jordan et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the therapies recited by Jordan et al., namely treating depression. One of. ordinary skill in the art would reasonably have expected success because ketamine is already known to be useful as an antidepressant.	This had been discussed above prior to the line-by-line reply (and also in prior replies to the OAs).

Thus the invention taken as a whole is prima facie obvious. Response to Argument: Applicant's arguments, filed July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the examiner has not considered the reply to the third office action. Arguments raised with respect to Jordan et al. are discussed previously. Arguments relating to Berman et al. are discussed under "further comments" below.	

Claims 3-5, 9-15, 20, 28, 37, and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Theobald et al. (US patent publication 2003/0049308, first published as PCT international publication W001/80837) Theobald et al. discloses a transdermal or transmucosal patch comprising nicotine and a further active substance, that is useful for treating nicotine dependency, for nicotine substitution, or for disaccustoming smokers. (p. 1, paragraphs 0002, 0003, and 0009) The additional active agent can include antidepressants or neuroleptics (antipsychotics), for example chlorpromazine, perphenazine, sulpride, clozapine, clomipramine, doxepin, risperidone, paroxetine, or fluvoxamine. (p. 2, paragraphs 00150017) Theobald et al. does not explicitly exemplify a method comprising administering said patch comprising nicotine, an antidepressant, and an antipsychotic. It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Theobald et al. using nicotine in combination with both an antidepressant and an antipsychotic. One of ordinary skill in the art would have been motivated to practice the invention in this manner because each of the additional agents (the antidepressant and the antipsychotic) is revealed individually by Theobald et al. to be useful in combination with nicotine for the treatment of nicotine addiction. Adding both of these agents at once to the disclosed invention is well within the ordinary and routine level of skill in the art and carries a reasonable expectation of success in achieving the desired therapeutic goal. Thus the invention taken as a whole is prima facie obvious. Response to Argument: Applicant's arguments, filed July 22, 2009, have been fully considered and not found to be persuasive to remove the rejection. Applicant argues that the reference is not enabling because paragraph 0008 rules out compositions with side effects. Presumably Applicant means by this that the patent would rule out using a neuroleptics because of the risk of extrapyramidal side effects, for example. However, this one paragraph should be taken in view of the later teaching in paragraphs 0015-0017 that neuroleptics can be used. Therefore one of ordinary skill in the art would read this reference as allowing the use of neuroleptics at a dose determined by one of ordinary skill in the art to be safe and well tolerated. Furthermore Applicant argues that the lack of further disclosure of how the active substance (e.g. neuroleptic or antidepressant) treats the psychological nicotine dependency, and no other reference is given. However, in order to enable a disclosed method the reference need merely disclose how to make and use the disclosed invention. There is no requirement to disclose how exactly the invention works. Therefore the rejection is deemed proper and made FINAL.	This had been discussed above prior to the line-by-line reply (and also in prior replies to the OAs). This had been discussed above prior to the line-by-line reply (and also in prior replies to the OAs).